TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS

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BY

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Dedicated to my family and teachers

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Dr. Richa Jindal

ABBREVIATIONS

µg	microgram/micrograms
%	Percentage
ASA	American Society of Anesthesiology
BMI	Body Mass Index
CPK	Creatinine phosphokinase
CNS	Central nervous system
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
ED	Effective dose
FDA	Food and Drug Administration
HR	Heart Rate
hr	hour
i.e	That is
IV	Intravenous
IVRA	Intravenous Regional Anesthesia
Kg	kilogram/kilograms
L	litre
MAP	Mean Arterial Pressure
mg	milligram/milligrams
ml	milliliter/millilitres
min	minute
MAC	Minimum Alveolar Concentration
mmol	millimol
mmHg	millimeters of Mercury
ng	nanogram/nanograms
NIBP	Non Invasive Blood Pressure
N_2O	Nitrous Oxide
O_2	Oxygen
sec	Second
SD	Standard Deviation
SpO_2	Peripheral Oxygen Saturation
SBP	Systolic Blood Pressure

ABSTRACT

Objective: To compare the efficacy of three different doses of dexmedetomidine pretreatment on incidence and severity of etomidate-induced myoclonus.

Methods: One hundred and twenty ASA I and II patients, aged 18-60 years scheduled for elective surgery under general anaesthesia were enrolled in this prospective, randomized, double blinded study after obtaining approval from institutional ethics committee. Patients were randomly allocated to four groups of 30 patients each. Group A was administered 10 ml of isotonic saline. Groups B, C and D were given dexmedetomidine 0.25, 0.5 and 1 μg kg^{-1} respectively diluted in 10 ml saline over 10 min. Then, 0.3 mg kg^{-1} etomidate was injected and the patients were observed for the incidence and grade of myoclonus. The hemodynamic parameters and adverse effects were also noted.

Results: The incidence of myoclonus in group A, B, C and D was 93%, 87%, 57% and 33% respectively. The incidence was comparable among groups C and D whereas it was significantly higher in group B. No patient in group D had severe myoclonus. Severity of myoclonus was lesser in group C as compared to group B. The incidence of bradycardia and hypotension was highest in group D whereas it was comparable among groups B and C. The incidence of tachycardia and hypertension was significantly higher in group A as compared to group D whereas it was comparable among other groups.

Conclusion: Dexmedetomidine is effective in reducing the incidence and severity of myoclonus in a dose dependent manner. Dexmedetomidine 0.5 μg kg^{-1} is the most effective dose since it is associated with suppression of myoclonus and results in minimal adverse effects.

Key words: Dexmedetomidine, Etomidate, Myoclonus

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INTRODUCTION

The most common technique for induction of general anaesthesia in the adult patients is the standard intravenous (IV) induction, which entails the administration of a rapid-acting IV anaesthetic, followed by a neuromuscular blocking drug. An ideal induction agent should have smooth induction, good hemodynamic stability, minimal respiratory and other side effects and rapid clearance. While there are many drugs that can be used intravenously to produce anaesthesia or sedation, the most common are: Midazolam, Thiopental, Etomidate, Ketamine and Propofol. Midazolam is used primarily for anxiolysis and amnesia or for conscious sedation. It has no pain relieving properties. Thiopental provides rapid onset and offset of action and cerebral protection but it causes a moderate dose dependent decrease in arterial blood pressure and respiratory drive. Ketamine has sympathomimetic effects that preserve cardiac function but it is associated with significant adverse psychological effects. Propofol is the most frequently used IV anaesthetic drug which provides rapid onset and offset of action. However, use of propofol is often complicated by hypotension.[1]

Etomidate is a short acting, non-barbiturate, imidazole derivative intravenous anesthetic agent, with unique properties like hemodynamic stability, favorable toxicity profile and pharmacokinetics enabling rapid induction and recovery after a single dose.[2] It is a potent hypnotic agent with minimal cardiovascular and respiratory adverse effects and provides better hemodynamic stability as compared to other induction agents. Etomidate does not trigger histamine release and is preferred in patients with underlying cardiac disease like coronary artery disease and compromised ventricular function, intracranial hypertension and in patients with shock.[2-4] At 0.3 mg kg^{-1} induction doses, etomidate does not cause significant alterations in heart rate, arterial pressures, right atrial pressure, systemic and pulmonary vascular resistance, stroke volume, cardiac index

and systemic blood flow.[3] So, it is a drug of choice for patients with valvular heart disease and in cardiac surgeries.[4]

Although, Etomidate has many advantages over other induction agents, but pain on induction, phlebitis, venous irritation, hemolysis and myoclonus are the commonly reported adverse effects.[3,5]

Doenicke et al have shown that the solubilizer propylene glycol is responsible for most of the side effects related to etomidate use. With new solvent, pain on injection, venous irritation and hemolysis has been virtually abolished. However, the incidence of myoclonus during induction is still as high as 50%–80%.[3,5-8]

Myoclonus is a medical sign characterised by a brief, involuntary, irregular twitching of a muscle or a group of muscles. It is different from clonus, which is rhythmic (regular). It can lead to muscle fiber damage, myalgias, elevated serum potassium levels and increased chances of reflux aspiration.[5] In addition, during the jerky movements ECG leads can get detached resulting in delay in monitoring.[2] Myoclonus is found to be associated with higher post induction hemodynamic variations in the form of increased heart rate, systolic blood pressure and mean blood pressure.[9] The consequences of myoclonus can be especially serious in non-fasting patients for emergency surgery, patients with open eye injury and poor cardiovascular reserve. Although etomidate-induced myoclonus is temporary in most patients, it is extremely harmful in those with hypertension, aneurysms, and coronary heart disease and can be life threatening.[5] The mechanism of these myoclonic movements is not clear, there are several suggested hypothesis:

Large doses of etomidate depress cortical activity of the brain before they depress subcortical activity due to the differences in the local cerebral blood flow.[6] So, myoclonus after etomidate is a phenomena of subcortical disinhibition like that of restless leg syndrome during sleep rather than an activation of epileptogenic focus. Some studies, however, have suggested that it may be a kind of seizure activity due to finding of increased delta

waves on EEG recording.[2,7] Therefore, it is suggested that caution should be taken before administering etomidate to unpremedicated patient with epilepsy or focal structural cortical lesions.[10]

A number of drugs like benzodiazepines, opioids, magnesium sulphate, IV lignocaine, propofol, thiopental, gabapentin and muscle relaxants have been investigated to reduce the rate and intensity of this adverse effect.[3,9,11-33] Each drug has variable effectiveness and contradictory results. Moreover, no drug is free of side effects and thus no single drug has achieved universal acceptance. However, considering that etomidate is a preferred agent in compromised hemodynamic cases and the necessity of prevention of myoclonus in these patients, the quest for an ideal drug to suppress the myoclonus continues.

Dexmedetomidine, an alpha2-adrenergic agonist is a relatively new drug, which has sedative and anxiolytic properties and is known for its analgesic potential owing to a reduction of sympathetic tone. Dexmedetomidine induces dose-dependent effects, ranging from minimal to deep sedation. Moreover, except at doses that cause very deep sedation or general anesthesia, the sedation is reversible. The patient can be easily roused to a lucent state, but when left undisturbed will fall back into a state very similar to natural sleep. These are unique properties among the sedative medications in common use. Dexmedetomidine does not impair the respiratory drive per se and seldom causes apnea. However, it has been shown to impair the respiratory responses to hypoxia and hypercapnia and can cause hemodynamic effects such as hypotension and bradycardia due to alpha-2 receptor stimulation in the central nervous system that inhibits sympathetic activity and reduces plasma epi-nephrine and norepinephrine levels.[34,35] This property has been reported to be useful in attenuating hemodynamic stress secondary to hyperadrenergic over-reactivity and agitation associated with delirium.[35]

This unique drug has also shown promising effect in reducing the incidence of etomidate induced myoclonus. Dey et al compared

dexmedetomidine in a dose of 0.5 μg kg^{-1} with midazolam 0.015 mg kg^{-1}; and found it to reduce the incidence and severity of myoclonus, but with increased incidence of adverse effects like hypotension and bradycardia.[36]

Luan et al used dexmedetomidine in two doses (0.5 μg kg^{-1} and 1 μg kg^{-1}) and the incidence of myoclonus was reduced, but with hypotension and bradycardia was more with a dose of 1 μg kg^{-1}. This was expected as the hypotension and bradycardia with dexmedetomidine has earlier been reported to be dose dependent.[7]

Gupta et al used dexmedetomidine (0.5, 0.8 and 1 μg kg^{-1}) as a premedication for the attenuation of hemodynamic responses of direct laryngoscopy and intubation. Patients showed a decrease in heart rate and blood pressure after dexmedetomidine infusion in a dose dependent manner.[37]

Kundra et al conducted an observational study to find a minimum dose of dexmedetomidine required for cessation of postspinal anesthesia shivering. The mean minimum effective dose at which none of the patients developed bradycardia or hypotension was found to be 0.258±0.024 μg kg^{-1} for patients with garde 3 shivering.[38]

There is paucity of literature to delineate the effective dose of dexmedetomidine with minimum side effects. Therefore, we designed a study to compare the effects of three different dexmedetomidine doses of 0.25 μg kg^{-1}, 0.5 μg kg^{-1} and 1 μg kg^{-1} for prevention of etomidate induced myoclonus during induction of anesthesia for elective surgeries and to find the effective dose of dexmedetomidine, so that adverse effects associated with higher doses of dexmedetomidine can be avoided.

PHARMACOLOGY- ETOMIDATE[39-50]:

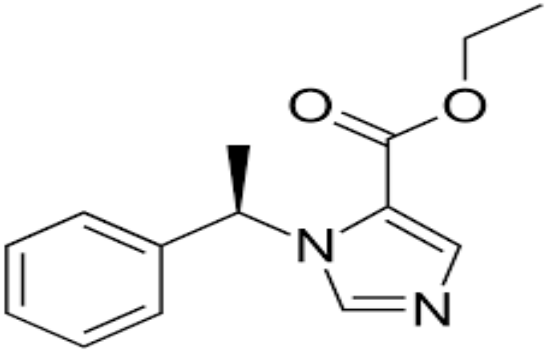
Generic name: Etomidate (General anaesthetic)

Dosage form: Injection

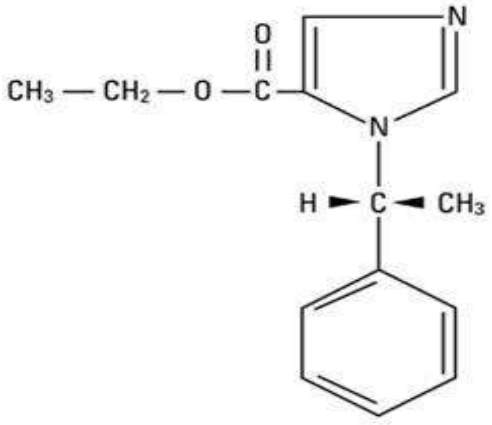
Ready to use vial: 10 ml of emulsion contains 20mg Etomidate

Excipients: Soya-Bean oil, medium-chain triglycerides, glycerol, egg lecithin, sodium oleate, water for injection

Etomidate is the Ethyl Ester of 1-((1R)-1-phenyl)-1H imidazole-5-carboxylic acid. It is an intravenous general anaesthetic of no analgesic property. It has a role as an intravenous anaesthetic and a sedative.



Chemical Structure of Etomidate



Structural formula of Etomidate

CLINICAL PHARMACOLOGY:

MECHANISM OF ACTION:

Etomidate appears to produce hypnosis, amnesia and inhibition of nociceptor responses, almost exclusively via actions at $GABA^A$ receptors (i.e. y–aminobutyric acid type A receptors)

Etomidate's remarkably benign cardiovascular and pulmonary effects are also likely the results of its selectivity. In comparison to clinical relevant concentrations of barbiturates, propofol and volatile anaesthetics modulate a broader array of $GABA^A$ receptor subtypes together with multiple other etomidate-insensitive ion channels found in both neurons and cardiovascular structures.

Most of $GABA^A$ receptors are composed of alpha, beta and gamma subunits. Each subunit polypeptide chain contains large N-terminal portion, four transmembrane regions and a short C-terminal extracellular portion. Amino acid residues of alpha and beta subunits contribute the binding site of GABA, whereas residues of alpha and delta subunits contribute to binding site of Benzodiazepines. Beta subunit is critical for action etomidate and propofol while alpha and beta in combination is critical for action of halothane and enflurane. Binding of barbiturates involves residues of beta subunits.

α-2 adrenergic receptors are also activated by etomidate. α-2 adrenergic action provides hemodynamic effect of etomidate. At high concentrations it activates transient receptor potential type A1 channels, a mechanism that may underlie pain during injection.

PHARMACOKINETICS AND METABOLISM:

Etomidate is approximately 75% plasma protein bound. The lipophylic properties promote the rapid movement through the blood brain barrier. The concentration in the cerebrospinal fluid approximately corresponds to the free, non protein bound drug concentration (25±3%). Renal dysfunction and chronic liver damage reduces protein binding of the drug. Cumulation of the drug has not been observed.

DISTRIBUTION:

Etomidate is highly lipid soluble thus, have a large central volume of distribution, 4.5 l kg^{-1}, and a very large peripheral volume of distribution 74.9 l kg^{-1}. The total apparent volume of distribution of about 4.6±2 l kg^{-1} is very large and points to considerable tissue uptake.

The volume of distribution of central compartment is greater than the total intravascular volume of plasma. Central compartment also includes the organs which are perfused by a large proportion of heart minute volume.

Thus, redistribution to the highly perfused area cause the initial fall in concentration after a single administration (initial half-life 1.3 to 4.5 minutes). The large volume of distribution ensures that the elimination half-life of 2.4 to 5 hr is relatively long in spite of a high rate of hepatic extraction.

METABOLISM:

Biotransformation is via ester hydrolysis of ethyl ester in the liver while a small proportion is subjected to oxidative N-dealkylation. All metabolites are pharmacologically inactive. Metabolism is via hepatic esterase, which hydrolyzes the drug to a carboxylic acid and an ethanol-leaving group.

EXCRETION:

The carboxylate metabolite is excreted via kidney in urine and a small amount in bile. The terminal metabolic half-life is 2 to 5 hrs. Total plasma clearance is 15-20 ml kg^{-1} min^{-1}. Elderly or ill patients often require decreased etomidate doses because of reduced protein binding and reduced clearance. The pharmacokinetic parameter for etomidate indicates its suitability for use as a continuous infusion, with a context-sensitive half-time shorter than that of propofol. However, adrenal toxicity precludes this application.

PHARMACODYNAMICS:

Etomidate acts as a hypnotic agent and is being used in general anaesthesia. Etomidate is a lipid soluble emulsion of soya oil, medium-chain triglycerides and egg lecithin, not containing any type of solubilising agents. Etomidate Lipuro allows a statistically significant reduction of the local side effects observed for aqueous formulations. The effect begins very rapidly early and duration of action is short lived as a result of redistribution and metabolism.

A single dose of 0.3 mg kg^{-1} leads to unconsciousness within 10 sec and anaesthesia of 3-5 min duration. In EEG latency period is 36 sec and the start of maximum effect is reached after 46 sec.

Typical induction doses of etomidate produce minimal changes in blood pressure and heart rate even in patients with cardiac disease. It does not have any effect on sympathetic responses to laryngoscopy and intubation, for which opioids are given beforehand as premedication.

DOSAGE:

The standard induction dose is 0.3 mg kg^{-1} and recovery is rapid due to redistribution to muscle and fat. Dose adjustment is done according to the clinical effect and individual response.

In general the effective hypnotic dose is between 0.15 and 0.3 mg kg^{-1} of body weight. Children up to the age of 15 years and elderly patients are given a single dose of 0.15 to 0.2 mg kg^{-1}, the exact dosage has to be adjusted according to the clinical effect.

In patients with liver cirrhosis and patients having been premedicated with neuroleptics dose has to be reduced.

Etomidate must be injected intravenously, slowly and in fractions if necessary. Paravenous injection will cause strong pain.

Pre-medication should be administered prior to etomidate to avoid the occurrence of myoclonus. In patients with manifest epilepsy or with an increased tendency of convulsion, it should be injected quickly, i.e. within a few seconds, in order to avoid slow diffusion of etomidate into the brain.

The good bioavailability of etomidate and its rapid distribution within the brain prevent activation of convulsions.

USES AND ADVANTAGES:

Etomidate has been proved useful for induction of general anaesthesia in patients undergoing cardiac surgery and in those with poor cardiac function. Etomidate also provide advantages in the settting of hemorrhagic shock.

Etomidate also been used as an agent for induction in critically ill patients. It has also been used as an induction agent in rapid sequence induction and intubation.

Etomidate causes modest reduction in hepatic blood flow, thus has minimal impact on pharmacology and metabolism of anesthetic agents. Cerebral perfusion pressure is maintained or increased during etomidate-induced anaesthesia.

ADVERSE EFFECTS:

Induction of anaesthesia can be accompanied by involuntary movements which may be mistaken for generalized seizure activity. In unpremedicated patients, involuntary muscle movements (myocloni) are frequently observed. This may be due to disinhibition of dienecephalic excitations. They can be prevented by premedication with opioids or benzodiazepines prior to administration of etomidate.

Pain on injection and incidence of thrombophlebitis is very high.

Nausea and vomiting is common in recovery period and is unpleasant.

Etomidate causes transient apnoea and can cause cough or hiccups. Thus, it is not ideally suited for insertion of LMA.

Etomidate inhibits 11-β-hydroxylase, an enzyme important in adrenal steroid production. A single induction dose blocks normal stress-induced cortisol production for 4-8 hours, and upto 24 hours in elderly patients. Continuous infusion in critically ill patients has been shown to increase

mortality. However, no increase in mortality has been identified following a single dose during induction of anaesthesia.

Isolated cases of hypersensitivity have been reported. Still, it is used as an agent of first choice in patients with history of allergy. Occasionally, it has been reported to cause transient apnoea, especially when combined with central depressant drugs and after administration of higher doses of etomidate.

Etomidate passes through placenta when used in pregnant patients. The APGAR scores of neonates are comparable with other hypnotic agents. The infantile cortical steroid synthesis inhibition effect is not known.

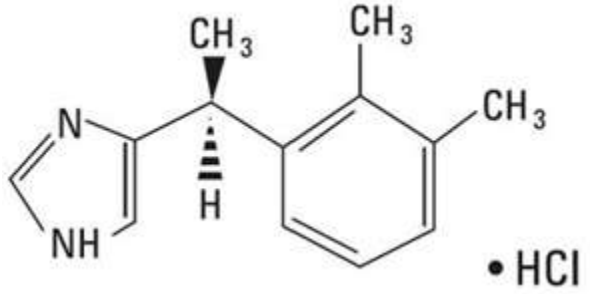
PHARMACOLOGY- DEXMEDITOMIDINE[51-57]

Generic name: Dexmedetomidine hydrochloride

Dosage form: Injection

Ready to use vial: Each ml contains 100 µg of Dexmedetomidine hydrochloride.

Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and ischemically described as (+)-4-(S)-[1-(2, 3-dimethylphenyl)ethyl]-1H-imidazolemonohydrochloride. It has a molecular weight of 236.7. It has the following structure with molecular formula C13H16N2HCl.



CLINICAL PHARMACOLOGY:

Dexmedetomidine, a second generation alpha-2 adrenergic receptor specific and pharmacologically active D-isomer of medetomidine, was first synthesized in late 1980's. Dexmedetomidine appears to mimic many of the actions of ideal sedative/analgesic agent with its wide spectrum of actions encompassing the entire perioperative period and then beyond that, into the critical care services. The food and drug administration (FDA) approved the use of Dexmedetomidine as an intensive care unit sedative in 1999 and its use for non intubated patients requiring sedation prior to or during surgical procedures in 2008. Dexmedetomidine has been growing in popularity and expanding its role in anaesthesia since then. Dexmedetomidine became alpha-2 agonist of choice, due to its greatest α2:α1 affinity (8 times greater than clonidine). This increased selectivity results in more predictable and effective sedation and analgesia with

fewer side effects. Dexmedetomidine has evolved as a panacea for various procedures with multiple promising delivery routes.

MECHANISM OF ACTION:

Dexmedetomidine induces sedation that resembles physiological sleep without causing respiratory depression. It produces analgesia by central, spinal and peripheral mechanisms. The pre-synaptic type of alpha-2 receptors regulates the release of nor-adrenaline and adenosine triphosphate through negative feedback mechanism. In CNS, the specific sites are locus coeruleus of upper brain stem and substantia gelatinosa in spinal cord. The supraspinal level of analgesia and sedation may be due to modulation of descending noradrenergic pathway originating in the main noradrenergic nucleus locus coeruleus. This supraspinal action could explain the prolongation of spinal analgesia after intravenous administration of Dexmedetomidine. The spinal level of anti nociceptive action seems to be through the substantia gelatinosa (Lamina II of Rexed in grey matter of spinal cord). It closes the gate at the dorsal horn to stimuli coming from peripheral A-delta and C fibres and also inhibits release of nociceptive humoral transmitters like substance P. It produces hyperpolarization of cell membrane. These mechanisms effectively suppress, both neuronal firing, as well as, release of neurotransmitter noradrenaline at the nerve terminals. This antinociceptive effect may explain the prolongation of sensory block when added to spinal anaesthetics.

Activation of postsynaptic alpha-2 adrenoreceptors is responsible for peripheral actions of the drug. Activation of alpha-2 receptors leads to dose dependent reduction in level of plasma catecholamines (maximum 89%), bradycardia and hypotension secondary to sympathetic inhibition of medullary vasomotor centre. Alpha-2 adrenoceptors do not have an active role in the respiratory centre, therefore, Dexmedetomidine throughout abroad range of plasma concentration (up to 8 ng ml^{-1}), has minimal effects on the respiratory system. Dexmedetomidine evokes a biphasic

blood pressure response. Alpha-2B adrenergic receptors are responsible for the initial short hypertensive phase while subsequent hypotension is mediated by alpha-2A adrenergic receptors. This direct effect on the peripheral vascular smooth muscle usually lasts for up to 10 minutes. It is observed that Dexmedetomidine does not alter the sweating threshold. There is a dose dependent decrease in vasoconstriction and shivering thresholds. Alpha-2 adrenergic agonists decrease the thermosensitivity at spinal and supraspinal sites by suppressing the neuronal conductance.

PHARMACOKINETICS AND METABOLISM:

Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2-0.7 µg kg^{-1} hr^{-1} when administered by intravenous infusion for 24 hours. Intravenous Dexmedetomidine infusion comes with a rapid distribution phase with a distribution half-life of approximately 6 minutes, a terminal elimination half-life of approximately 2 hours and steady-state volume of distribution of approximately 118 litres. The pharmacokinetic profile of Dexmedetomidine is not altered by age.

DISTRIBUTION:

Plasma protein binding of Dexmedetomidine is approx. 94% (mostly to albumin). The fraction of Dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

METABOLISM:

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged drug excreted in urine (approx. 95%) and faeces. Biotransformation involves both direct glucuronidation in liver as well as cytochrome P450 meditated metabolism. The major metabolic pathways of Dexmedetomidine are : direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6 with a minor role of CYP1A2, CYP2E1, CYP2D6 and CYP2C19) of Dexmedetomidine to generate 3-hydroxy-Dexmedetomidine, the glucuronide of 3-hydroxy-

Dexmedetomidine and 3-caboxy-Dexmedetomidine and N-methylation of Dexmedetomidine to generate 3-hydroxy N-methyl-Dexmedetomidine, 3 carboxy N-methyl-Dexmedetomidine and Dexmedetomidine-N-methyl O glucuronide.

PHARMACODYNAMICS:

Dexmedetomidine induces sedation by decreasing activity of noradrenergic neurons in the locus coeruleus in the brain stem, thereby increasing activity of inhibitory gamma-aminobutyric acid neurons in the ventrolateral preoptic nucleus. Sedation by Dexmedetomidine mirrors natural sleep and it provides less amnesia than benzodiazepines. It also has analgesic effects at the spinal cord level and other supraspinal sites. Thus, unlike other hypnotic agents like propofol, it can be used as an adjunct medication to help decrease the opioid requirements of people in pain while still providing similar analgesia.

CLINICAL ACTIONS:

Central

a. Sedation, hypnosis, anxiolysis
b. Analgesia
c. Bradycardia and hypotension

Peripheral

a. Decreased gastrointestinal secretions, inclusive of saliva and decreased gastrointestinal motility
b. Constriction of vascular and other smooth muscles
c. Inhibition of renin-angiotensin system and decreased release of renin
d. Increased glomerular filtration rate, increased excretion of Na, water and thus diuresis
e. Decreased intra-ocular pressure
f. Decreased insulin release from the pancreas
g. Decreased platelet aggregation

h. Decreased shivering threshold (by approx. 2◦C)

INDICATIONS AND USES:

- Dexmedetomidine when used as adjunct to general anaesthesia, attenuates stress response to tracheal intubation or extubation. Optimal dose for attenuating pressor response seems to be 1 μg kg^{-1} with lesser doses not being effective.
- Dexmedetomidine when given as a premedication decreases oxygen consumption intraoperatively and post-operatively.
- As an adjuvant to general anaesthesia, it has minimum alveolar concentration (MAC) reducing and opiate sparing properties, which helps in decreasing the inhalation anaesthetic, IV anaesthetic and opioid requirements by up to 90%.
- In patients receiving Dexmedetomidine, the reduction in heart rate and blood pressure product and myocardial oxygen demand reduce subsequent myocardial ischemia and infraction. This is beneficial for cardiac patients.
- As an adjuvant in peripheral nerve block and intravenous regional anaesthesia (IVRA): Dexmedetomidine when added to local anesthetics or given IV prolongs the duration of sensory block of local anesthetics during peripheral nerve block.
- Dexmedetomidine has been found to provide neuroprotective effect by decreasing cerebral blood flow without interfering either with cerebral metabolic rate or intra cranial pressure.
- Intensive Care Unit Sedation: Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.
- Procedural Sedation: Dexmedetomidine is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

DOSAGE:

For adult patients: a loading infusion of 1 µg kg^{-1} given over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 µg kg^{-1} given over 10 minutes may be suitable. The maintenance infusion is generally initiated at 0.6 µg kg^{-1} hr^{-1} and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 µg kg^{-1} hr^{-1}. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

For patients over 65 years of age: a loading infusion of 0.5 µg kg^{-1} over 10 minutes. For adult patients with impaired hepatic function: a dose reduction should be considered.

CONTRAINDICATIONS:

- Dexmedetomidine is not recommended for microvascular free flap procedures, as alpha-2 agonists may cause direct vasoconstriction and reduction in flap blood flow.
- Patients with hepatic dysfunction may require a lower dose of Dexmedetomidine than healthy subjects to achieve a similar response, given the extensive hepatic metabolism of Dexmedetomidine.
- Dexmedetomidine can cross the placenta and should be used cautiously during pregnancy or breast feeding.
- Dexmedetomidine is contraindicated in patients with shock, heart block and hypotension.

ADVERSE EFFECTS:

- Hypotension
- Respiratory depression
- Bradycardia
- Hypertension
- Tachycardia
- Hypoxia

AIMS AND OBJECTIVES

To study comparative efficacy with three different doses of dexmedetomidine pretreatment on incidence and severity of etomidate-induced myoclonus.

REVIEW OF LITERATURE

Etomidate is an unique drug used for induction of general anaesthesia due to its stable hemodynamic effects. The first report on etomidate was published in 1965. Intially developed as an antifungal agent, its potent hypnotic activity was observed and appeared significantly safer than barbiturates. It was introduced into clinical practice in 1972 and emerged in clinical literature soon afterwards.[58] Stimulation of the hypothalamic-pituitary adrenal axis is one of the most important hormonal reactions to critical illness. The use of etomidate has been challenged in this context because it causes reversible adrenal insufficiency. Though, the adrenal insufficiency is reversible but still increased hospital morbidity has been reported in critically ill patients by Majesko et al in their randomized controlled trail.[59] Adrenal suppression is found to last for 6-8 hours in patients following single induction dose of etomidate and more than 24 hours following etomidate infusion.[58] So, etomidate continues to be used as a single injection induction dose in hemodynamically unstable patients as it is less likely to cause hypotension.[59] A randomised controlled trial in patients undergoing cardiac surgery revealed that propofol causes a 34% greater reduction in MAP from baseline after induction of anaesthesia than etomidate and more frequent use of vasopressors was found with propofol, proving the superior haemodynamic profile of etomidate.[60] But pain on injection, phlebitis and myoclonus are the most common side effects of etomidate. The occurrence of phlebitis and injection pain have been abolished by the fat emulsion, but the myoclonus still remains an unsolved problem. The incidence of myoclonus has been reported to be as high as 50-80% and is a cause for concern.[3]

The incidence and severity of myoclonus has been reported to be dependent on dose and speed of injection. Priming dose of etomidate given before induction dose appears to reduce the incidence of myoclonus.[61] Still, the mechanism of its occurrence and ideal agent for its prevention remains elusive.

It is a pity that a drug which offers so many advantages in terms of immunological safety, cardiovascular stability, rapid recovery and favorable pharmacokinetic profile, is beset by a complication that severely limits its use. Thus, efforts continue to be made in order to mitigate etomidate induced myoclonus, which has a potential to compromise patient safety.

Mullick et al in 2018, conducted a study on one hundred and eighty nine surgical patients to compare the effect of priming versus slow injection and compared it with control group. They found priming dose of 0.03 mg kg^{-1} etomidate, 1 min before induction dose to be more effective in reducing the incidence of myoclonus than slow injection of induction dose only but the severity of myoclonus was found not to be affected.[61]

Similarly Doenicke et al in 1999, performed three studies to find the effect of priming and smaller doses of etomidate on myoclonus and found that smaller induction doses as well as smaller priming doses are associated with lesser incidence of myoclonus.[6]

Various drugs have also been studied for their ability to suppress myoclonus which includes benzodiazepines, opioids, magnesium sulphate, IV lignocaine, gabapentine, thiopental, propofol, parecoxib sodium and pretreatment with muscle relaxants.[3,9,11-33,62]

Sedighinejad et al in 2016, conducted study on two hundred and eighty four patients scheduled for elective orthopedic surgery to compare the effect of midazolam, magnesium sulphate, remifentanil and low dose etomidate and found low dose etomidate before induction dose to be most effective followed by remifentanil, midazolam and then magnesium sulphate in terms of reducing both incidence and severity of myoclonus.[11]

Pre-treatment with midazolam, opioids and combination of both has been widely used and found to be effective in mitigating myoclonic movements associated with etomidate use.

Salim et al in 2015, conducted a study on two hundred and fifty patients scheduled for elective surgery to find effectiveness of midazolam 0.05 mg

kg^{-1} administered ninety seconds before induction with etomidate and reported that midazolam is very effective in reducing incidence (15.45%) as well as severity of myoclonus (Grade 3 only in 1.6% patients).[12]

Hwang et al in 2008, performed comparative evaluation of midazolam with remifentanil as pre treatment agents for reducing etomidate induced myoclonus on ninety adult patients undergoing surgery. They found that incidence of myoclonus was lower in both the groups but there was no significant difference between the two groups. Remifentanil related side effects like bradycardia and chest wall rigidity were found in some patients so, they proposed that midazolam is probably a better choice than remifentanil for reducing myoclonus.[13]

Su Ri et al investigated the appropriate dose of remifentanil for preventing myoclonus without side effects. Incidence of myoclonus caused by etomidate bolus was significantly reduced with a 2 ng ml^{-1} effect site concentration of remifentanil without causing chest wall rigidity.[14]

Similarly Parkash et al conducted a randomised trial on two hundred and ten surgical patients. Incidence and severity of myoclonus was found less in fentanyl (2 μg kg^{-1}) and midazolam (0.03 mg kg^{-1}) combination group than fentanyl (2 μg kg^{-1}) and midazolam (0.03 mg kg^{-1}) alone. They also concluded that myoclonus is associated with higher post induction hemodynamic variation in the form of increase in heart rate, systolic blood pressure and mean blood pressure from pre-induction values.[9]

Isitemiz et al have also used combination of fentanyl in a dose of 0.5 μg kg^{-1} and midazolam 0.015 mg $kg^{-1}$and reported that the combination of the two agents reduced the incidence of myoclonus by 60%.[3]

Alka et al used combination of butorphanol 0.02 mg kg^{-1} and midazolam 1 mg to compare with fentanyl and midazolam combination and reported that the butorphanol and midazolam combination reduced incidence and severity of myoclonus by 3.3% than fentanyl and midazolam combination. They also observed that the dose of etomidate for induction is decreased by butorphanol in combination with midazolam.[15]

Another study on butorphanol was done by Zhao et al and comparison was done with fentanyl. One hundred and fifty patients were randomly assigned into 3 groups of fifty each and they found butorphanol to be effective and safe in reducing etomidate induced myoclonus incidence by 78% from control placebo group and 20% from fentanyl group without significant side effects.[16]

Pal et al performed a comparative study with two different doses of butorphanol (0.02 mg kg^{-1} and 0.04 mg kg^{-1}) to find a minimum effective dose to prevent etomidate induced myoclonus. They concluded that 0.02 mg kg^{-1} is as effective as 0.04 mg kg^{-1} dose with statistically insignificant difference in incidence and severity of myoclonus between two groups.[17]

Wang et al performed meta-analysis of nine randomized controlled trials and concluded that pre treatment with opioids before injecting etomidate was effective for preventing etomidate induced myoclonus and reduce the intensity without any adverse effect.[18]

Stockham et al conducted a study on fentanyl to find an optimal pre-induction dose which eliminates haemodynamic changes and side effects during induction and intubation with etomidate.They found an increasing incidence of apnoea and decreasing incidence of myoclonus and injection pain with increasing dose of fentanyl and suggested that 500 µg is an ideal pretreatment dose prior to anaesthesia induction with etomidate.[19]

A prospective, randomized, double blind study was conducted by Mayank et al on one hundred patients to study the effect of nalbuphine 0.2 mg kg^{-1} and found it to be effective in reducing incidence of etomidate induced myoclonus by 52% than normal saline group.[20]

Another study on nalbuphine was done by Bisht et al in comparison to fentanyl to assess the severity of pain, incidence and severity of myoclonus and serum creatinine phosphokinase (CPK) levels after giving etomidate injection for induction. They found that nalbuphine is more effective than fentanyl in the prevention of etomidate induced myoclonus and pain with the minimum rise in CPK levels.[21]

Khteishat et al compared the impact of preinduction with fentanyl, ketamine or midazolam on the frequency and intensity of etomidate induced myoclonic muscle movements and concluded that fentanyl 2 $\mu g kg^{-1}$ administration before etomidate induction of general anaesthesia decreased significantly the frequency and severity of etomidate induced myoclonic muscle movements by 57.3% from ketamine 2 mg kg^{-1} group and 6.2% from midazolam 0.015 mg kg^{-1} group.[22]

Another study done by Kelsaka et al concluded that men experience increased incidence of myoclonus than women and pretreatment with remifentanil 1 μg kg^{-1} is effective in reducing the incidence of myoclonus after etomidate injection by 63.3% than placebo group without any side effects like sedation, apnea, nausea or pruritis.[23]

Wang et al studied oxycodone 0.1 mg kg^{-1} and fentanyl 1 μg kg^{-1} for this purpose and reported the incidence in oxycodone group as 0.0%.[24]

Zhu et al performed meta-analysis of six randomized control trials and concluded that preinjection of dezocine is effective in lowering the incidence and severity of etomidate induced myoclonus without increasing etomidate induced dizziness and nausea.[25]

The major problem with both midazolam and opioids is that these drugs result in respiratory depression and desaturation especially at high doses. This has prompted researchers to try other drugs with more desirable properties to reduce etomidate induced myoclonus.

Singh et al studied effect of 2% lignocaine (1ml) or midazolam (1ml) as a premedication in reducing the incidence and severity of myoclonus and found both of them efficacious.[26]

Gupta et al found that IV lignocaine in a dose of 1 mg kg^{-1} reduced the incidence of myoclonus by 10% as compared to placebo group in a study conducted on two hundred patients who were divided into four groups to receive placebo and three different doses of lignocaine.[27]

Another study done by Jyothi et al to compare three different doses of 2% lignocaine proved that 50 mg and 60 mg both doses are effective in

reducing the severity of myoclonus induced by etomidate without causing side effects.[28]

Guler et al investigated the influence of pretreatment with magnesium and two doses of ketamine and concluded that magnesium 2.48 mmol administered 90 sec before the induction of anaesthesia with etomidate is effective in reducing the severity of myoclonus but ketamine failed to reduce the incidence of myoclonus.[29]

A randomized clinical trial on parecoxib sodium pretreatment reduces myoclonus after etomidate concluded that pretreatment with IV parecoxib sodium 40 mg significantly reduced the incidence and severity of etomidate induced myoclonus without significant side effects.[62]

Mensure et al noted that oral gabapentin in dose of 800 mg and 1200 mg as premedication to be effective in reducing the incidence of myoclonus as compared to placebo group. However, oral gabapentin in a dose of 400mg was found not to superior to placebo in suppressing etomidate induced myoclonus.[30]

Liu et al conducted a prospective, double blind, randomized controlled study on three sixty- three patients scheduled for a short duration, painless gastrointestinal endoscopy in which pretreatment with different doses of propofol was done before induction with etomidate and found that the incidence and severity of etomidate induced myoclonus was lower in patients receiving pretreatment with propofol as compared to patients receiving etomidate alone.[31]

Nooraei et al concluded that low dose atracurium priming (20% of ED95 x kg) could effectively suppress etomidate induced myoclonus.[32]

Dexmedetomidine is now a days being widely used in anaesthesia and critical care practice due to many desirable properties. It has sedative and analgesic properties without causing any respiratory depression. Many investigators have found it to prevent etomidate induced myoclonus as well.[2,5,7]

Mizrak et al conducted a prospective, randomized, double - blind study comparing the effect of pretreatment with dexmedetomidine 0.5 μg kg^{-1}, thiopental 1 mg kg^{-1} and saline on incidence of etomidate induced myoclonus and postoperative pain at 30 minutes. They observed incidence and intensity of myoclonus significantly lower in dexmedetomidine and thiopental groups than in control group but postoperative pain score at thirty minutes was significantly higher in thiopental group than dexmedetomidine and control group.[33]

Dey et al compared 0.5 μg kg^{-1}dexmedetomidine and 0.015 mg kg^{-1} midazolam for prevention of etomidate –induced myoclonus and noted that incidence of myoclonus was reduced by 17.5% in patients treated with dexmedetomidine.[36]

Du et alhave also reported the efficacy of dexmedetomidine to reduce incidence as well as severity of myoclonus due to etomidate.[5]

Though the effectiveness of dexmedetomidine in suppressing myoclonus has been widely reported but the appropriate dose for this is still under debate.

Dixit et al[2] administered dexmedetomidine in a dose of 1 μg kg^{-1} while Dey et al[36] used 0.5 μg kg^{-1}.Luan et al compared 0.5 μg kg^{-1} with 1 μg kg^{-1} and found dexmedetomidine at these doses to be effective. The incidence of hypotension and bradycardia was found to be higher with 1 μg kg^{-1} of dexmedetomidine.[7]

Dexmedetomidine has been used in doses ranging from 0.25-1.0 μg kg^{-1} for suppression of laryngoscopic response and there is benefit in choosing the smallest dose as the adverse effects are dose dependent.[63] Despite a thorough search of literature, we could not find any study where dexmedetomidine 0.25 μg kg^{-1} was used for prevention of etomidate induced myoclonus.

MATERIALS AND METHODS

SOURCE OF DATA

The study was conducted in a prospective, randomized, double blinded manner in the department of Anesthesiology, DMCH Ludhiana after obtaining clearance from hospital ethics committee. 120 adult patients of either sex between age group 18 to 60 years belonging to ASA grade I or II scheduled for elective surgery under general anaesthesia were randomly allocated to either of four study groups of 30 patients each.

GROUP ALLOCATION:

Patients were randomly allocated to either of four groups as per computer generated random numbers which were kept in a sealed envelope and opened at the end of study. The study drug was prepared in a coded manner by an anaesthesia resident who did not participate in the management of patients.

Group A patients were administered 10ml of isotonic saline.

Group B patients were administered dexmedetomidine 0.25 µg kg^{-1} in 10 ml isotonic saline over 10 mins.

Group C patients were administered dexmedetomidine 0.5 µg kg^{-1} in 10 ml isotonic saline over 10 mins.

Group D patients were administered dexmedetomidine 1 µg kg^{-1} in 10 ml isotonic saline over 10 mins.

METHOD OF COLLECTION OF DATA

NUMBER OF CASES

Total number of cases proposed to be studied were 120 with 30 patients in each group.

INCLUSION CRITERIA:

Patients of either sex between age group 18 to 60 years belonging to ASA grade I or II with BMI <30 kg m^{-2} and scheduled for elective surgery under general anaesthesia were included in the study.

EXCLUSION CRITERIA:

1. Patients with BMI>30 kg m^{-2}.
2. Patients with Bradycardia (HR < 60/min), having heart blocks, on β– blockers or having pacemakers.
3. Known case of hypoadrenalism or patients on steroid medication.
4. H/o asthma, chronic cough or upper respiratory infection two weeks before surgery.
5. H/o any neurologic disease.
6. H/o any psychiatric disorders.
7. Pregnant and lactating patients.
8. H/o any drug allergy.
9. Patients having uncontrolled diabetes or hypertension.
10. Patients who had received benzodiazipines or opioids within the previous 24 hrs.
11. Any evidence of sepsis.

PREANAESTHETIC CHECK UP

A thorough preanaesthetic check up was conducted preoperatively one day prior to surgery comprising of detailed history, general physical and systemic examination. Routine investigations like complete hemogram, prothrombin time/INR, urine routine, renal function tests, random blood sugar, chest X-ray and ECG were obtained.

PREMEDICATION

All patients were kept nil per oral for at least six hours prior to surgery. Patient were counselled and explained regarding the surgical procedure to

allay anxiety. No pharmacological anxiolytic therapy was administered. All patients were given Tab Ranitidine 150 mg a night prior to the surgery.

ANAESTHESIA TECHNIQUE

After arrival of patient to the operating room, routine monitoring such as electrocardiogram (ECG), non-invasive blood pressure (NIBP), heart rate (HR) and arterial oxygen saturation (SpO_2) were started and baseline parameters were recorded. A 20-gauge Intravenous (IV) cannula was secured and I/V fluid infusion started. Before anaesthesia induction, all patients were administered study drug over 10 min as per group allocation. Group A was infused 10ml of isotonic saline, while Groups B, C and D were infused 0.25, 0.5 and 1.0 µg kg^{-1}dexmedetomidine in 10 ml isotonic saline respectively over 10 min. Once the infusion was completed, this time was labelled as '0' and 0.3 mg kg^{-1}etomidate was injected intravenously over a period of 30 sec.

Patients were observed continuously for myoclonus for 2 min by an anaesthesia resident blinded to study drug received. Myoclonic movements were defined as involuntary, short duration muscular contractions leading to short observable movements in parts of the body.

The intensity of myoclonus was graded as:[1]

0- No myoclonus
1- mild myoclonus (short movements of a body segment, e.g. a finger or a wrist only)
2- moderate myoclonus (mild movements of two different muscles, e.g. face and leg)
3- severe myoclonus (intense clonic movements in two or more muscle groups, e.g. fast adduction of a limb)

After administration of etomidate and evaluation for myoclonus, all patients were injected with 2 µg kg^{-1} fentanyl and isoflurane 1% was started. To facilitate tracheal intubation injection atracurium 0.5 mg kg^{-1}

was given. Trachea was intubated with appropriate sized cuffed tube. After ensuring correct endotracheal tube placement, all patients were mechanically ventilated and maintained on O_2:N_2O and Isoflurane. Intraoperatively management of anaesthesia was as per the discretion of anaesthetist managing the case.

Hemodynamic parameters were recorded every 1 minute for initial 10 minutes and then every 5 minutes till the end of 60 minutes. Hypotension was defined as systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg and an intravenous injection of 6mg ephedrine was administered. Bradycardia was defined as HR <50 beats per minute and any episode of bradycardia was treated with I/V injection of 0.5 mg atropine. An episode of tachycardia (defined as heart rate > 20% of baseline value) and hypertension (defined as blood pressure > 20% of baseline value), lasting for more than a minute, was controlled by a bolus of fentanyl (1 µg kg^{-1}) rounded off to multiple of ten. Another bolus of 0.5 µg kg^{-1} fentanyl was repeated after 15 minutes if the episode of heart rate and blood pressure did not revert to normal. More fentanyl boluses were given if the attending anaesthesiologist who is blinded to the study infusion felt the need for it.

OUTCOME

The following parameters were statistically analyzed:

1) Incidence of etomidate induced myoclonus.

2) Grading of etomidate induced myoclonus.

3) Incidence of any adverse effects.

STATISTICAL ANALYSIS

Data was described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using ANOVA. For comparing

categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency was less than 5. A probability value (p value less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

The present study was conducted in a randomized, double blinded manner in the Department of Anesthesiology, DMCH Ludhiana on a total of 120 adult patients of either sex, between age group 18 to 60 years belonging to ASA grade I or II who were scheduled for elective surgery under general anaesthesia.

The study aimed to evaluate the comparative efficacy of three different doses of dexmedetomidine pretreatment on incidence and severity of etomidate- induced myoclonus. Patients were divided into four groups of 30 patients each, who were administered study drug diluted to make a volume of 10 ml over 10 min.

Group A - Patients were given 10ml of isotonic saline.

Group B - Patients were treated with dexmedetomidine 0.25 µg kg^{-1}.

Group C - Patients were treated with dexmedetomidine 0.5 µg kg^{-1}.

Group D - Patients were treated with dexmedetomidine 1 µg kg^{-1}.

Once the infusion was completed, this time was labelled as '0' and 0.3 mg kg^{-1} etomidate was injected intravenously over a period of 30 sec. Patients were observed continuously for myoclonus for 2 min. Hemodynamic parameters were recorded every 1 min for initial 10 min and then every 5 min till the end of 60 min. The observations of our comparative study are as follows:

DEMOGRAPHIC PROFILE

Table 1: Mean age distribution

	GROUP A		GROUP B		GROUP C		GROUP D		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (yrs)	44.07	12.99	39.67	11.60	39.53	9.74	44.23	10.72	0.190

Mean age of patients in group A was 44.07±12.99 years, group B was 39.67±11.60 years, group C was 39.53±9.74 years and group D was 44.23±10.72 years. There was no statistically significant difference among the four groups with respect to age, p value being 0.190 (Table 1, Figure 1).

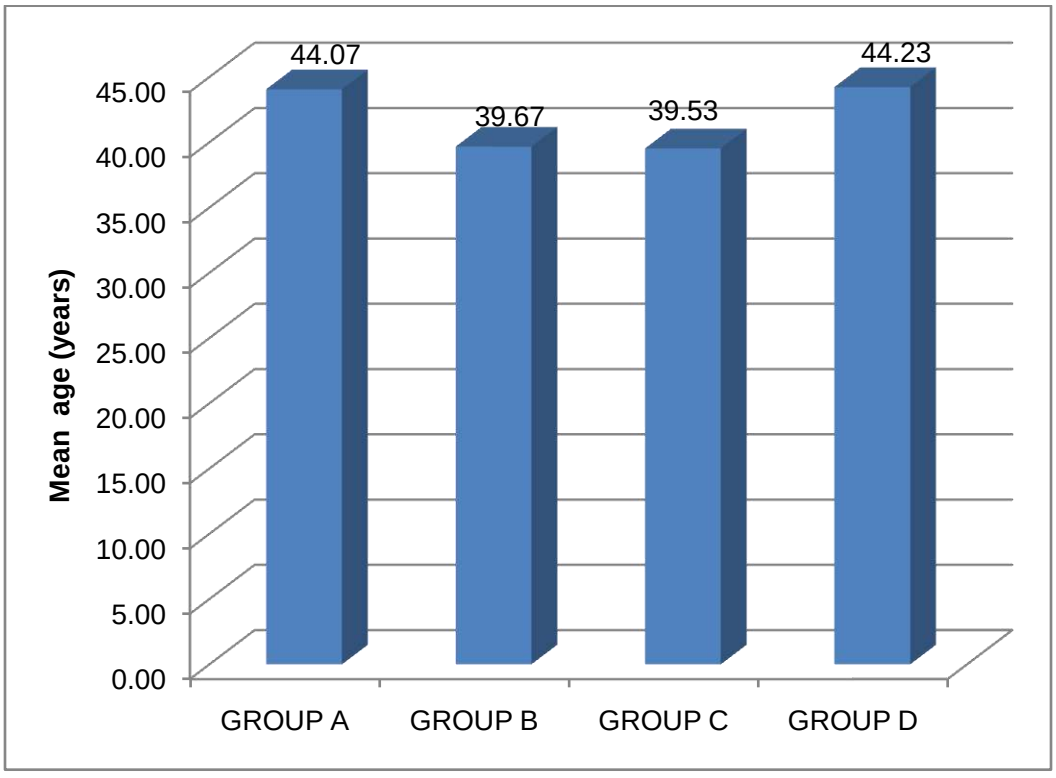


Figure 1: Mean age distribution

Table 2: Sex distribution

		Group				Total	p-value
		A	B	C	D		
Sex	F	10	13	14	17	54	0.338
	M	20	17	16	13	66	
Total		30	30	30	30	120	

All the four groups were comparable with respect to sex distribution, with p value 0.338. (Table 2, Figure 2)

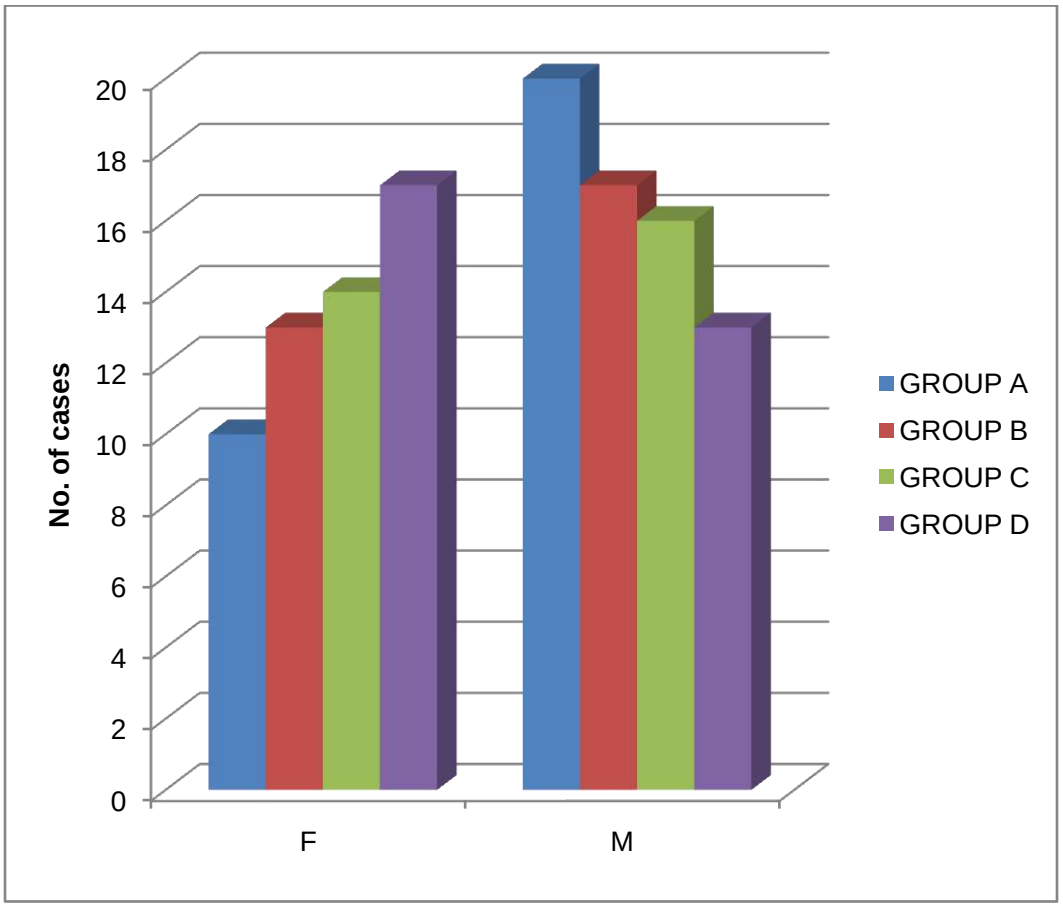


Figure 2: Sex distribution

Table 3: Mean weight

	GROUP A		GROUP B		GROUP C		GROUP D		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Weight (kg)	71.07	10.91	70.07	10.88	70.60	8.41	67.00	10.52	0.412

Mean weight of patients in group A was 71.07±10.91 kg, group B was 70.07±10.88 kg, group C was 70.60±8.41 kg and group D was 67.00±10.52 kg. The difference of mean weight was statistically insignificant (p value 0.412) (Table 3, Figure 3)

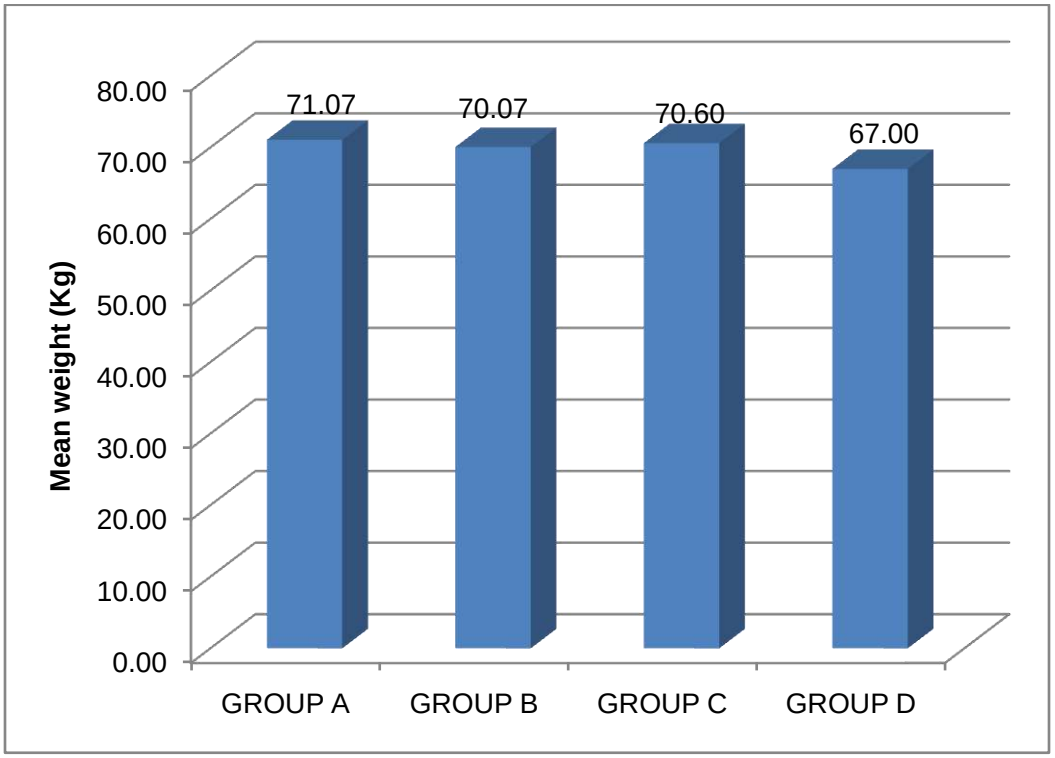


Figure 3: Mean weight

Table 4: Mean height

	GROUP A		GROUP B		GROUP C		GROUP D		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Height (cm)	166.20	9.31	174.16	45.30	175.34	45.05	166.62	9.93	0.579

Mean height of patients in group A was 166.20±9.31 cm, group B was 174.16±45.30 cm, group C was 175.34±45.05 cm and group D was 166.62±9.93 cm. The difference of mean height was statistically insignificant (p value 0.579) (Table 4, Figure 4)

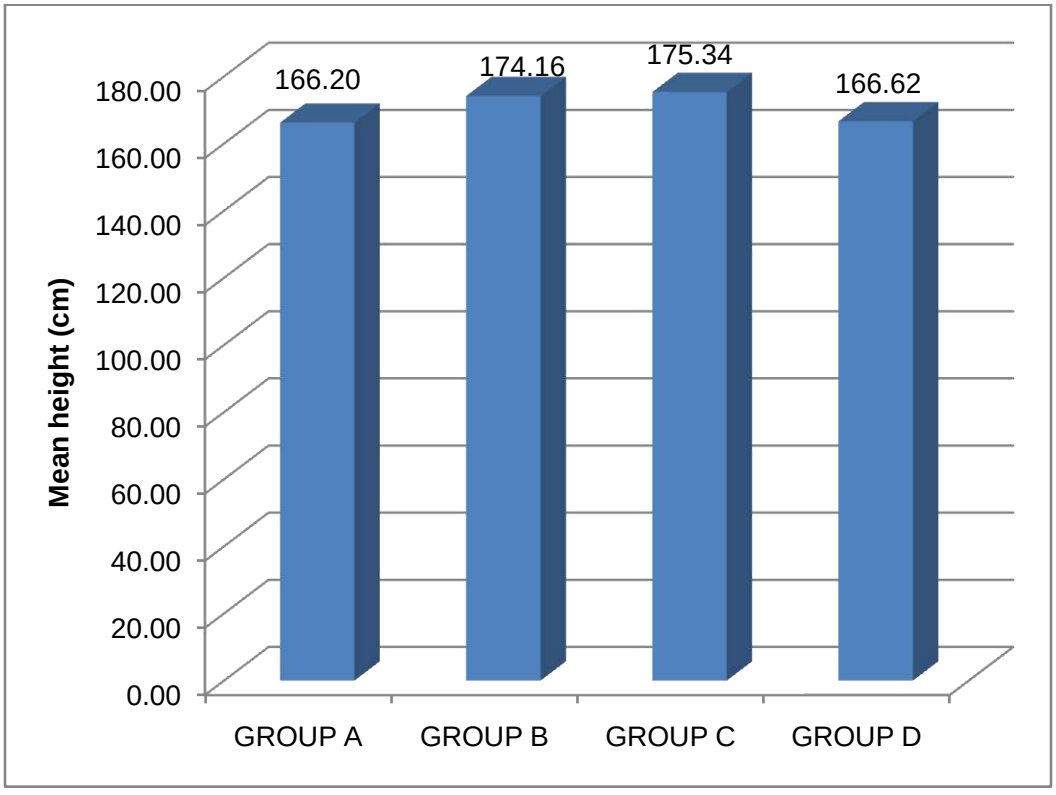


Figure 4: Mean height

Table 5: Mean BMI

	GROUP A		GROUP B		GROUP C		GROUP D		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BMI	25.04	3.45	25.02	3.19	25.52	2.62	24.78	2.62	0.809

Mean BMI in group A was 25.04±3.45 kg m^{-2}, group B was 25.02±3.19 kg m^{-2}, group C was 25.52±2.62 kg m^{-2} and group D was 24.78±2.62 kg m^{-2}. The difference in mean BMI of patients in all the four groups was statistically insignificant with a p value of 0.809. (Table 5, Figure 5)

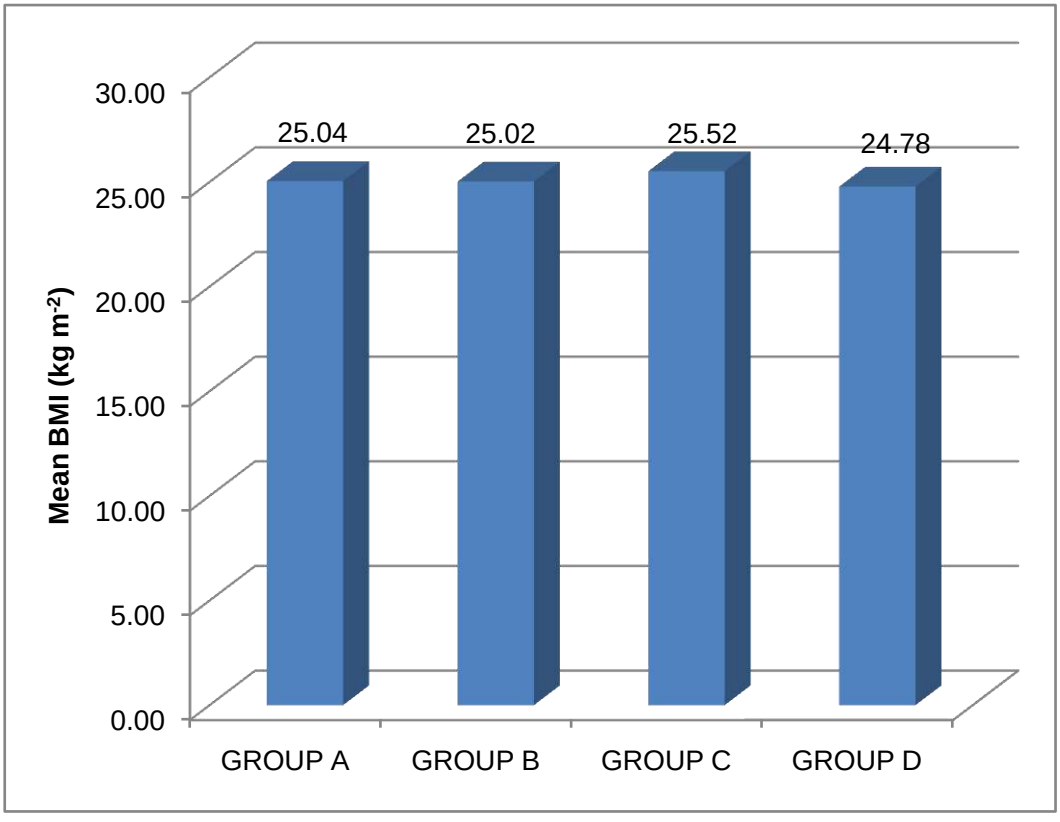


Figure 5: Mean BMI

Table 6: ASA physical status

		Group				Total	p-value
		A	B	C	D		
ASA Grading	I	16	14	15	18	63	0.760
	II	14	16	15	12	57	
Total		30	30	30	30	120	

The difference in ASA distribution in all the four groups was statistically not significant. (p value 0.760) (Table 6, Figure6)

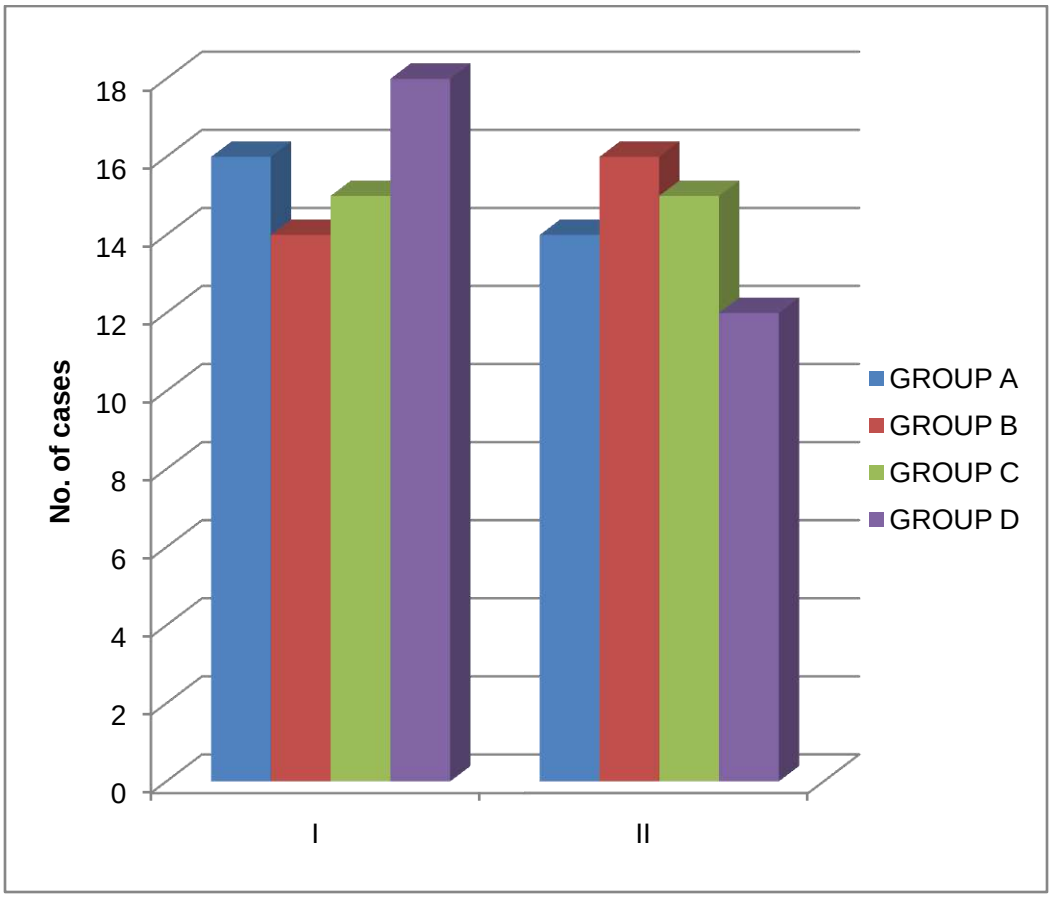


Figure 6: ASA physical status

Table 7: Mean heart rate (HR) after administration of study drug

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Baseline	83.70	16.11	85.70	15.69	88.83	14.42	84.70	9.93	0.537	0.588	0.166	0.786	0.396	0.786	0.264
0 min	83.07	14.98	74.63	14.53	72.10	13.15	64.77	8.51	0.000	0.014	0.001	0.000	0.453	0.004	0.031
1 min	84.27	13.38	74.70	14.90	71.13	14.19	64.33	10.55	0.000	0.006	0.000	0.000	0.303	0.003	0.051
2 min	86.27	14.54	74.40	13.59	72.27	16.64	64.03	11.16	0.000	0.001	0.000	0.000	0.560	0.005	0.026
3 min	88.63	17.05	74.63	13.69	75.13	16.77	68.03	13.42	0.000	0.001	0.001	0.000	0.900	0.098	0.075
4 min	88.43	16.25	75.50	13.10	75.70	15.82	69.87	14.24	0.000	0.001	0.001	0.000	0.959	0.146	0.132
5 min	87.77	16.96	77.63	15.37	75.53	16.87	72.70	17.16	0.004	0.020	0.005	0.001	0.625	0.252	0.510
6 min	87.57	18.78	80.17	15.55	77.80	16.04	73.80	13.75	0.011	0.078	0.021	0.001	0.571	0.129	0.339
7 min	87.27	17.79	80.50	14.33	79.70	16.00	72.70	12.69	0.005	0.090	0.058	0.000	0.840	0.051	0.079
8 min	84.53	16.87	79.27	11.27	79.63	16.11	73.40	20.33	0.081	0.218	0.251	0.010	0.931	0.170	0.145
9 min	83.13	16.80	78.70	10.17	77.17	12.73	72.20	16.91	0.037	0.237	0.112	0.004	0.682	0.084	0.185
10 min	81.50	16.52	78.47	10.80	77.73	12.29	72.10	15.02	0.071	0.398	0.294	0.010	0.838	0.077	0.118
15min	81.10	15.82	79.13	11.76	76.23	12.71	71.73	12.75	0.044	0.569	0.161	0.008	0.402	0.034	0.194
20 min	79.93	13.46	77.30	11.06	75.43	13.35	73.07	13.34	0.209	0.429	0.177	0.041	0.575	0.204	0.477
25 min	81.40	11.99	76.43	11.00	74.33	13.57	72.33	12.06	0.031	0.117	0.027	0.005	0.506	0.195	0.526
30 min	80.63	11.85	76.57	10.40	74.10	13.06	73.07	11.82	0.069	0.185	0.034	0.015	0.421	0.254	0.736
35min	80.40	11.99	75.53	10.78	72.67	12.74	71.27	10.00	0.013	0.102	0.010	0.002	0.333	0.151	0.636
40min	80.50	11.44	75.50	10.43	72.27	12.19	70.63	9.18	0.003	0.077	0.004	0.001	0.252	0.086	0.562
45min	80.13	12.57	75.30	10.57	71.53	12.54	71.13	11.19	0.012	0.114	0.005	0.004	0.217	0.172	0.895
50min	80.80	9.33	75.60	9.75	71.17	11.05	71.10	11.54	0.001	0.057	0.001	0.000	0.103	0.098	0.980
55min	80.87	9.59	74.90	9.63	70.73	10.66	70.73	10.40	0.000	0.024	0.000	0.000	0.112	0.112	1.000
60min	81.53	9.94	75.27	9.52	70.73	10.34	70.40	9.76	0.000	0.016	0.000	0.000	0.079	0.059	0.896

The mean baseline HR was 83.70±16.11, 85.70±15.69, 88.83±14.42 and 84.70±9.93 in group A, B, C and D respectively. No statistically significant difference was observed in all the four groups (p value 0.537)

The mean HR at time '0' was 83.07±14.98, 74.63±14.53, 72.10±13.15 and 64.77±8.51 in group A, B, C and D respectively. On inter group comparison, the mean HR at time '0' was found to be lowest in group D as compared to group B, C and A. The mean HR was statistically similar among group B vs C.

The mean HR remained below the baseline in group B, C and D at most time intervals whereas in group A, it was near the baseline. The mean HR was found to be lowest in group D and it was statistically insignificant among group B vs C. (Table 7, Figure 7)

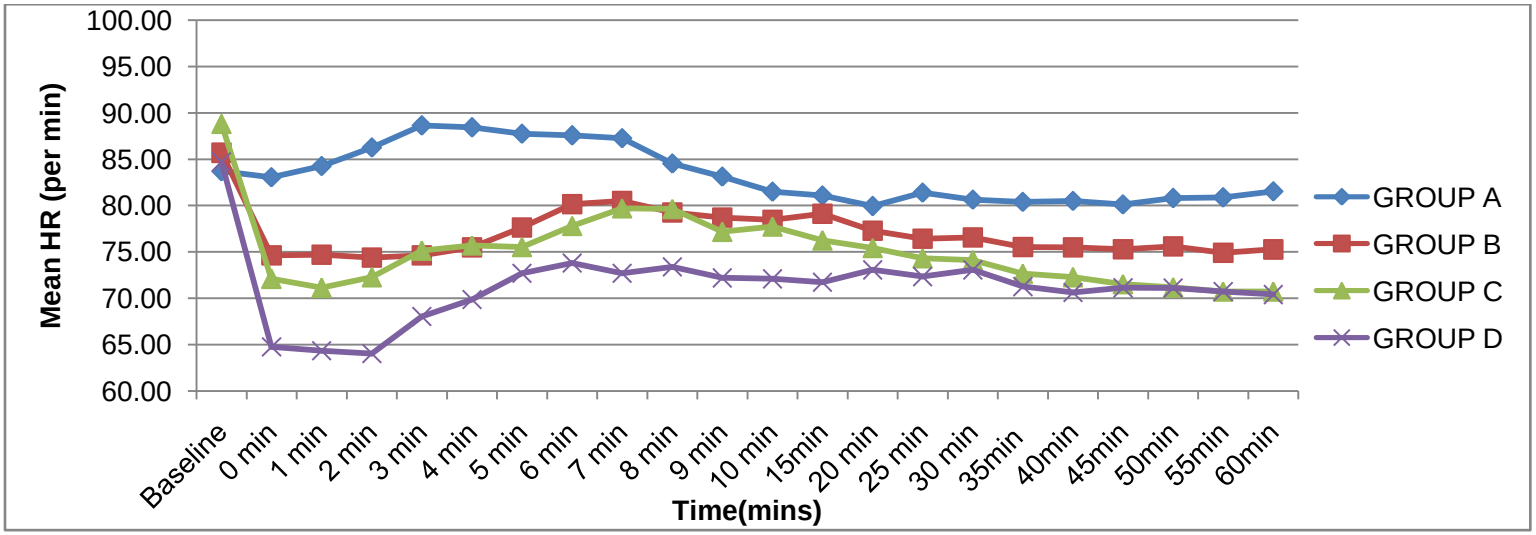


Figure 7: Mean heart rate (HR) after administration of study drug

Table 8: Mean percentage variation of HR from baseline values

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
0 min	0.39	7.02	12.55	9.47	18.39	10.07	22.79	11.81	0.000	0.000	0.000	0.000	0.022	0.000	0.083
1 min	-1.47	7.32	12.02	14.91	19.33	12.73	23.24	14.25	0.000	0.000	0.000	0.000	0.027	0.001	0.234
2 min	-4.60	16.74	12.20	13.47	18.16	14.61	23.56	14.87	0.000	0.000	0.000	0.000	0.126	0.004	0.166
3 min	-7.43	20.76	11.69	14.34	14.67	16.87	19.03	16.19	0.000	0.000	0.000	0.000	0.503	0.101	0.327
4 min	-6.66	14.23	10.46	15.66	13.67	18.59	16.50	18.83	0.000	0.000	0.000	0.000	0.465	0.170	0.519
5 min	-6.20	18.52	8.20	16.30	14.09	18.03	13.74	18.32	0.000	0.002	0.000	0.000	0.203	0.232	0.939
6 min	-6.03	21.48	5.02	17.75	10.80	21.95	12.14	16.34	0.002	0.030	0.001	0.000	0.254	0.161	0.791
7 min	-5.20	17.30	4.24	18.92	8.75	21.06	13.40	15.56	0.001	0.048	0.004	0.000	0.343	0.055	0.328
8 min	-2.02	16.77	5.98	13.00	8.82	20.86	13.20	19.68	0.011	0.085	0.020	0.001	0.539	0.120	0.344
9 min	-0.55	18.07	6.42	13.79	11.68	16.98	14.36	17.31	0.004	0.107	0.005	0.001	0.223	0.067	0.533
10 min	1.35	18.14	6.55	15.64	11.09	16.10	14.60	14.61	0.013	0.215	0.021	0.002	0.279	0.056	0.402
15min	1.80	17.12	5.72	16.83	12.86	16.08	14.91	13.51	0.006	0.343	0.008	0.002	0.085	0.028	0.621
20 min	3.08	14.98	8.22	13.81	13.96	15.61	13.23	15.00	0.019	0.184	0.005	0.009	0.137	0.194	0.849
25 min	1.21	14.46	8.83	17.13	15.33	15.30	14.14	13.60	0.002	0.054	0.000	0.001	0.100	0.178	0.762
30 min	1.68	16.84	8.80	15.21	15.50	15.62	13.28	12.92	0.003	0.073	0.001	0.004	0.091	0.257	0.573
35min	1.97	17.11	10.21	14.51	17.16	15.07	15.28	12.08	0.001	0.033	0.000	0.001	0.072	0.188	0.624
40min	2.17	14.68	10.10	15.20	17.63	13.92	16.08	10.48	0.000	0.027	0.000	0.000	0.035	0.093	0.662
45min	2.65	15.83	10.28	15.12	18.41	15.10	15.72	10.87	0.000	0.042	0.000	0.001	0.030	0.145	0.470
50min	1.42	14.74	9.85	15.13	18.66	14.54	15.71	11.91	0.000	0.023	0.000	0.000	0.017	0.112	0.420
55min	1.30	15.26	10.67	14.87	19.10	14.76	16.11	10.73	0.000	0.011	0.000	0.000	0.022	0.136	0.410
60min	0.56	15.08	10.34	14.44	19.00	15.14	16.42	10.63	0.000	0.008	0.000	0.000	0.018	0.094	0.476

The mean percentage increase in HR from baseline was seen in group A and fall was seen in other groups. This difference was highly significant among group A vs D and group A vs C but this was non significant among group B vs C, B vs D and C vs D at most time intervals. (Table 8, Figure 8)

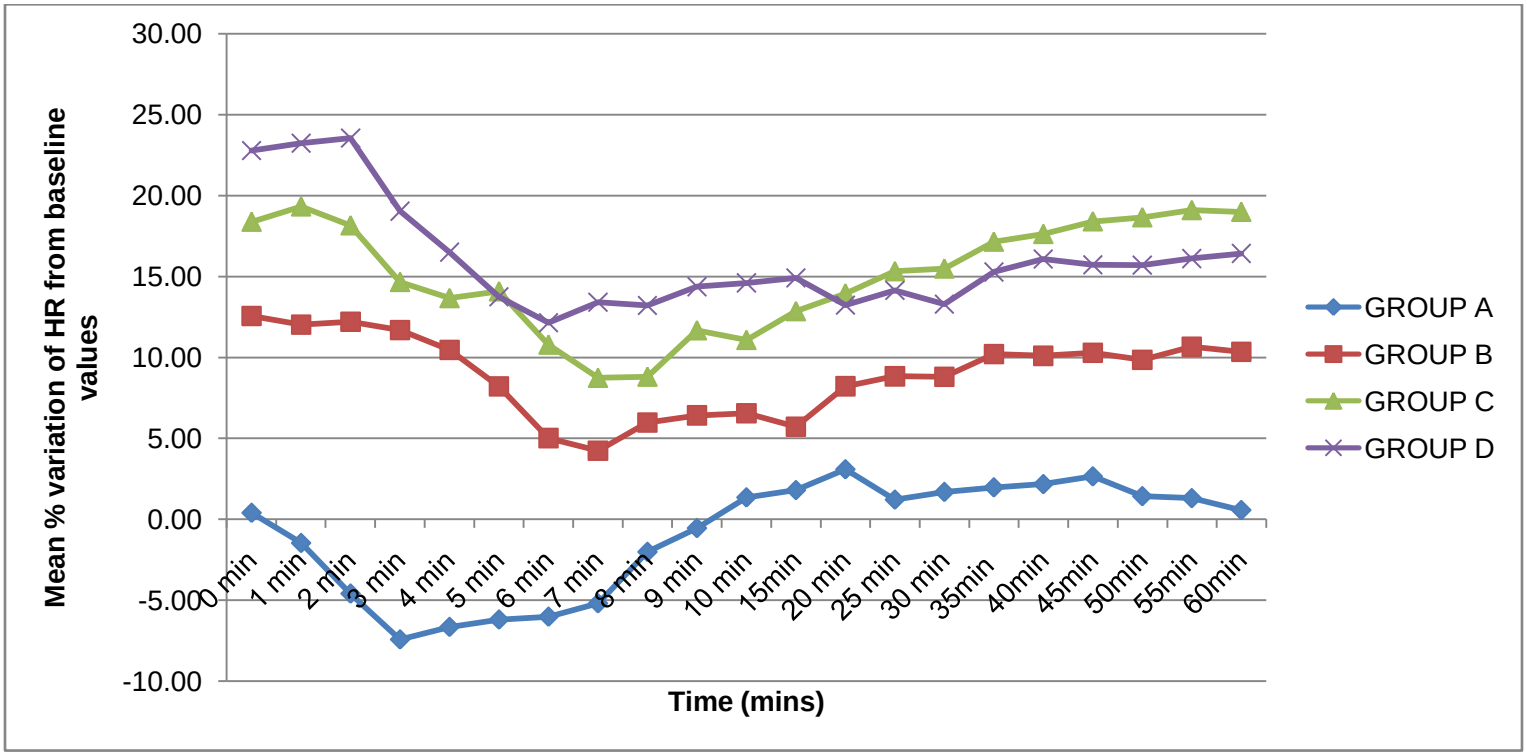


Figure 8: Mean percentage variation of HR from baseline values

Table 9: Mean SBP after administration of study drug

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Baseline	128.57	8.70	127.03	8.58	130.33	7.47	129.30	8.12	0.468	0.472	0.408	0.731	0.123	0.288	0.628
0 min	132.20	17.17	121.47	13.69	120.70	14.02	118.00	16.80	0.003	0.008	0.005	0.001	0.848	0.388	0.501
1 min	129.77	15.73	119.70	16.88	120.67	13.69	113.50	19.63	0.003	0.021	0.036	0.000	0.822	0.151	0.098
2 min	130.07	18.06	116.33	14.19	119.13	17.60	113.87	19.01	0.002	0.003	0.016	0.000	0.532	0.582	0.241
3 min	131.73	21.10	121.80	19.48	116.27	15.39	119.07	20.74	0.015	0.049	0.002	0.012	0.269	0.585	0.576
4 min	131.37	19.96	121.17	21.05	116.43	18.85	116.97	18.75	0.014	0.047	0.004	0.005	0.353	0.410	0.917
5 min	131.33	22.29	124.20	18.07	118.53	20.28	121.53	24.45	0.124	0.199	0.022	0.079	0.307	0.630	0.588
6 min	132.27	23.18	123.87	16.65	121.57	15.25	127.53	24.61	0.197	0.112	0.044	0.369	0.662	0.486	0.258
7 min	130.90	19.34	122.47	15.68	129.23	21.96	125.20	19.86	0.322	0.094	0.739	0.256	0.178	0.585	0.421
8 min	127.23	18.64	123.20	13.71	127.80	19.28	122.33	23.53	0.595	0.415	0.909	0.323	0.353	0.861	0.270
9 min	125.50	20.07	121.20	13.04	124.60	15.42	116.73	22.73	0.238	0.362	0.849	0.065	0.471	0.344	0.097
10 min	124.97	20.94	121.10	14.51	120.07	12.44	119.83	18.57	0.621	0.379	0.265	0.243	0.814	0.773	0.958
15min	119.17	13.82	121.47	15.14	120.83	14.28	116.03	18.67	0.537	0.569	0.680	0.438	0.875	0.180	0.236
20 min	121.33	12.49	122.80	14.52	119.83	14.72	115.63	14.86	0.239	0.689	0.683	0.122	0.419	0.053	0.254
25 min	124.17	14.35	126.40	12.60	122.50	12.78	117.00	18.24	0.087	0.557	0.661	0.061	0.305	0.015	0.149
30 min	124.13	17.19	121.20	14.50	122.93	13.70	114.83	16.12	0.097	0.463	0.764	0.021	0.664	0.113	0.044
35min	126.30	18.32	123.10	15.17	121.60	12.73	119.30	15.68	0.368	0.429	0.246	0.085	0.710	0.347	0.569
40min	129.97	17.13	120.87	15.21	120.67	13.06	117.33	11.65	0.007	0.016	0.014	0.001	0.957	0.344	0.372
45min	128.27	14.10	120.13	16.25	119.27	12.99	118.17	12.65	0.025	0.027	0.015	0.006	0.812	0.589	0.763
50min	127.20	15.93	119.80	14.82	119.77	12.28	118.03	12.19	0.056	0.041	0.041	0.012	0.993	0.623	0.630
55min	125.97	16.38	119.27	13.66	118.90	11.77	117.23	14.13	0.087	0.068	0.054	0.018	0.920	0.577	0.648
60min	121.60	15.34	117.60	13.70	118.37	12.68	118.17	14.58	0.688	0.275	0.377	0.348	0.834	0.877	0.956

The mean baseline SBP in Group A was 128.57±8.70 mmHg, Group B was 127.03±8.58 mmHg, Group C was 130.33±7.47 mmHg and Group D was 129.30±8.12 mmHg. The difference in mean baseline SBP was statistically not significant (p value 0.468)

The mean SBP at time 0 was 132.20±17.17 mmHg in Group A, 121.47±13.69 mmHg in Group B, 120.70±14.02 mmHg in Group C and 118.00±16.80 mmHg in Group D. On inter group comparison SBP at time '0' was found to be lowest in group D as compared to group B and C. The mean SBP was statistically similar among group B vs C, B vs D and C vs D.

The mean SBP remained below the baseline in group B, C and D at all time intervals where as in group A, it was near the baseline. The mean SBP was found to be lowest in group D and it was statistically insignificant among groups B vs C, B vs D, C vs D. (Table 9, Figure 9)

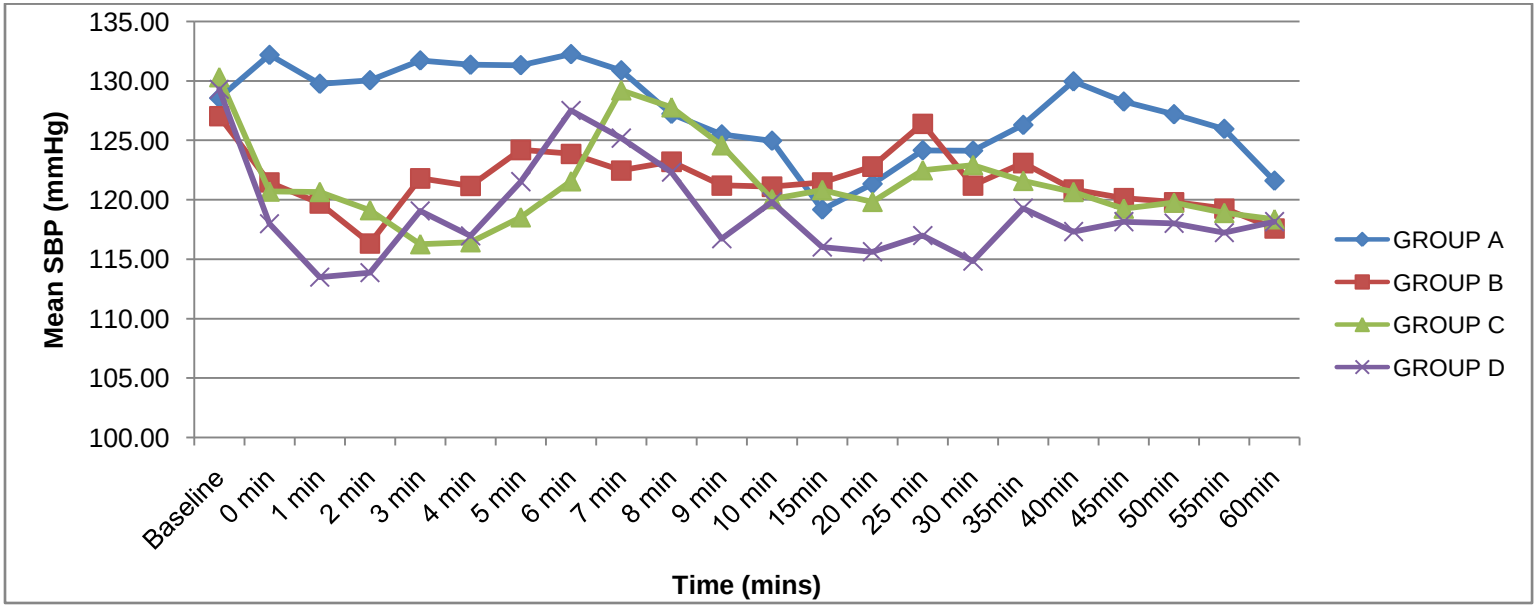


Figure 9: Mean SBP after administration of study drug

Table 10: Mean DBP after administration of study drug

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Baseline	80.20	9.17	77.10	11.01	77.57	9.08	77.57	8.58	0.577	0.209	0.285	0.285	0.849	0.849	1.000
0 min	81.20	12.10	73.37	15.44	73.83	14.13	73.80	11.42	0.072	0.025	0.035	0.034	0.893	0.900	0.992
1 min	80.10	12.98	71.73	13.75	74.53	12.33	70.07	15.34	0.029	0.019	0.117	0.005	0.428	0.637	0.207
2 min	79.57	14.37	68.53	12.60	73.33	15.30	68.00	11.11	0.004	0.002	0.075	0.001	0.169	0.878	0.127
3 min	82.07	16.96	72.73	17.84	70.90	11.21	72.77	12.38	0.019	0.017	0.004	0.017	0.634	0.993	0.628
4 min	82.27	18.82	72.00	14.87	70.73	14.81	73.03	12.85	0.019	0.012	0.005	0.023	0.752	0.797	0.566
5 min	80.53	13.86	76.57	15.82	71.83	16.45	77.37	21.73	0.275	0.374	0.053	0.478	0.289	0.857	0.216
6 min	80.20	18.41	74.83	15.62	76.00	13.91	80.17	19.12	0.486	0.221	0.338	0.994	0.790	0.224	0.342
7 min	79.57	13.58	73.83	15.18	79.10	17.53	75.77	13.06	0.391	0.140	0.904	0.327	0.175	0.617	0.389
8 min	79.67	14.59	73.20	12.54	78.13	16.90	73.90	17.29	0.292	0.108	0.701	0.151	0.219	0.861	0.291
9 min	75.50	10.99	72.77	13.46	73.80	12.63	70.23	15.87	0.487	0.430	0.623	0.129	0.765	0.464	0.303
10 min	79.33	17.46	72.27	14.45	69.70	11.23	72.97	11.94	0.058	0.053	0.009	0.080	0.479	0.847	0.368
15min	71.17	12.00	71.90	15.99	71.70	12.54	70.77	12.32	0.987	0.831	0.877	0.908	0.954	0.742	0.786
20 min	73.23	9.80	71.80	13.87	70.80	11.52	69.37	8.60	0.588	0.619	0.399	0.181	0.728	0.399	0.619
25 min	76.70	11.07	76.20	11.23	74.10	10.75	71.17	12.27	0.225	0.865	0.376	0.061	0.475	0.088	0.319
30 min	75.27	14.01	70.27	11.63	73.83	12.75	72.43	12.95	0.484	0.135	0.667	0.395	0.285	0.515	0.674
35min	79.93	12.71	75.53	13.34	72.33	10.75	74.17	11.86	0.102	0.165	0.017	0.070	0.312	0.665	0.562
40min	79.90	13.06	71.83	12.89	71.77	12.10	71.40	10.57	0.020	0.012	0.011	0.008	0.983	0.891	0.908
45min	79.70	11.13	73.60	11.14	70.40	10.67	73.80	9.23	0.009	0.027	0.001	0.033	0.243	0.942	0.215
50min	79.27	10.98	72.87	12.14	71.73	8.85	73.73	9.60	0.031	0.020	0.006	0.043	0.676	0.749	0.461
55min	78.17	14.80	73.33	11.72	74.00	12.26	73.00	10.00	0.337	0.131	0.193	0.107	0.834	0.917	0.754
60min	75.60	11.19	70.90	11.53	73.17	10.31	71.73	9.94	0.353	0.093	0.383	0.167	0.416	0.765	0.607

The mean baseline DBP in Group A was 80.20±9.17 mmHg, Group B was 77.10±11.01 mmHg, Group C was 77.57±9.08 mmHg and Group D was 77.57±8.58 mmHg. The difference in mean baseline DBP was statistically not significant (p value 0.577)

The mean DBP at time 0 was 81.20±12.10 mmHg in Group A, 73.37±15.44 mmHg in Group B, 73.83±14.13 mmHg in Group C and 73.80±11.42 mmHg in Group D. On inter group comparison, the mean DBP at time '0' was statistically similar among groups B, C and D.

The mean DBP remained below the baseline in all the groups at most time intervals and the difference was not statistically significant except among groups A vs B, A vs C and A vs D from 1-4 min. (Table 10,Figure 10)

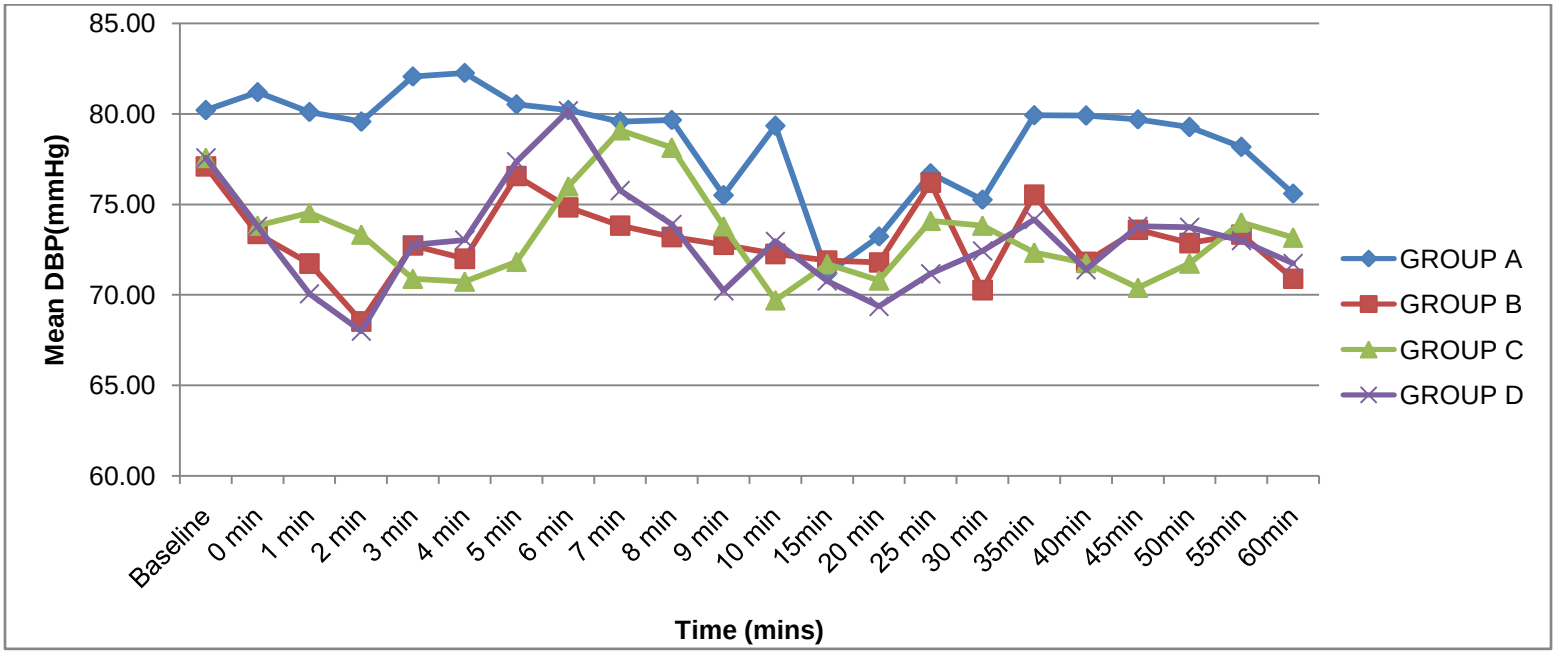


Figure 10: Mean DBP after administration of study drug

Table 11: Mean MAP after administration of study drug

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Baseline	95.20	12.92	96.70	7.68	99.37	6.08	97.53	7.54	0.339	0.517	0.074	0.314	0.250	0.719	0.429
0 min	100.23	11.03	93.40	13.84	93.40	14.24	92.87	14.92	0.117	0.054	0.054	0.038	1.000	0.879	0.879
1 min	100.07	14.19	92.03	12.75	94.20	13.54	87.93	17.67	0.016	0.036	0.124	0.002	0.568	0.281	0.100
2 min	98.83	14.55	88.57	10.63	92.37	16.16	87.90	14.82	0.013	0.006	0.080	0.003	0.302	0.856	0.225
3 min	102.00	16.43	92.83	18.08	89.57	13.62	92.30	15.32	0.019	0.028	0.003	0.020	0.429	0.897	0.508
4 min	102.83	17.78	90.80	17.50	90.27	16.60	92.23	14.84	0.013	0.006	0.004	0.016	0.902	0.740	0.650
5 min	101.57	16.76	97.77	18.02	91.53	17.12	95.40	21.59	0.204	0.427	0.038	0.199	0.194	0.621	0.419
6 min	103.47	20.72	96.40	15.98	95.07	14.56	98.93	20.82	0.301	0.136	0.077	0.338	0.778	0.592	0.413
7 min	101.37	14.32	94.77	14.80	100.60	18.45	96.97	15.42	0.331	0.109	0.852	0.284	0.156	0.591	0.376
8 min	98.87	15.69	93.83	12.06	99.93	16.77	94.83	19.68	0.392	0.234	0.800	0.339	0.149	0.812	0.228
9 min	95.43	13.96	93.23	12.34	95.23	13.12	90.83	17.14	0.567	0.551	0.957	0.214	0.588	0.516	0.234
10 min	97.93	19.58	92.83	13.71	91.70	10.96	93.00	13.67	0.373	0.185	0.106	0.200	0.768	0.965	0.735
15min	91.60	13.06	92.30	14.40	93.87	12.06	89.80	13.51	0.695	0.839	0.510	0.601	0.649	0.468	0.238
20 min	92.30	11.48	92.77	12.76	92.40	12.65	88.53	10.21	0.470	0.879	0.974	0.220	0.905	0.168	0.208
25 min	96.03	12.57	96.40	10.79	95.17	11.59	89.67	14.53	0.131	0.909	0.788	0.050	0.702	0.038	0.090
30 min	95.97	14.66	91.10	10.89	95.27	11.63	90.03	13.81	0.194	0.145	0.833	0.076	0.211	0.748	0.117
35min	99.13	14.45	94.77	12.22	93.87	10.90	94.13	12.94	0.338	0.185	0.111	0.130	0.784	0.847	0.935
40min	100.07	14.31	92.83	11.56	93.13	11.57	90.77	10.45	0.021	0.022	0.028	0.003	0.923	0.508	0.449
45min	99.03	12.25	92.30	12.47	90.57	11.68	92.80	10.99	0.037	0.030	0.007	0.044	0.573	0.871	0.467
50min	99.23	12.85	91.87	12.48	91.90	9.57	91.77	10.00	0.026	0.013	0.013	0.012	0.991	0.973	0.964
55min	97.13	15.04	92.33	10.64	93.07	10.54	90.87	10.95	0.214	0.122	0.190	0.044	0.812	0.635	0.477
60min	94.07	12.80	89.33	11.43	92.60	11.19	90.77	11.39	0.425	0.120	0.629	0.278	0.283	0.637	0.546

The mean baseline MAP in Group A was 95.20±12.92 mmHg, Group B was 96.70±7.68 mmHg, Group C was 99.37±6.08 mmHg and Group D was 97.53±7.54 mmHg. The difference in mean baseline MAP was statistically not significant (p value 0.339)

The mean MAP at time 0 was 100.23±11.03 mmHg in Group A, 93.40 ±13.84 mmHg in Group B, 93.40±14.24 mmHg in Group C and 92.87±14.92 mmHg in Group D. On inter group comparison, the mean MAP at time '0' was statistically similar among all the groups except group A vs D.

The mean MAP remained below the baseline in all the groups at most time intervals. On inter group comparison, the mean MAP was statistically similar in all the groups at most time intervals. (Table 11,Figure 11)

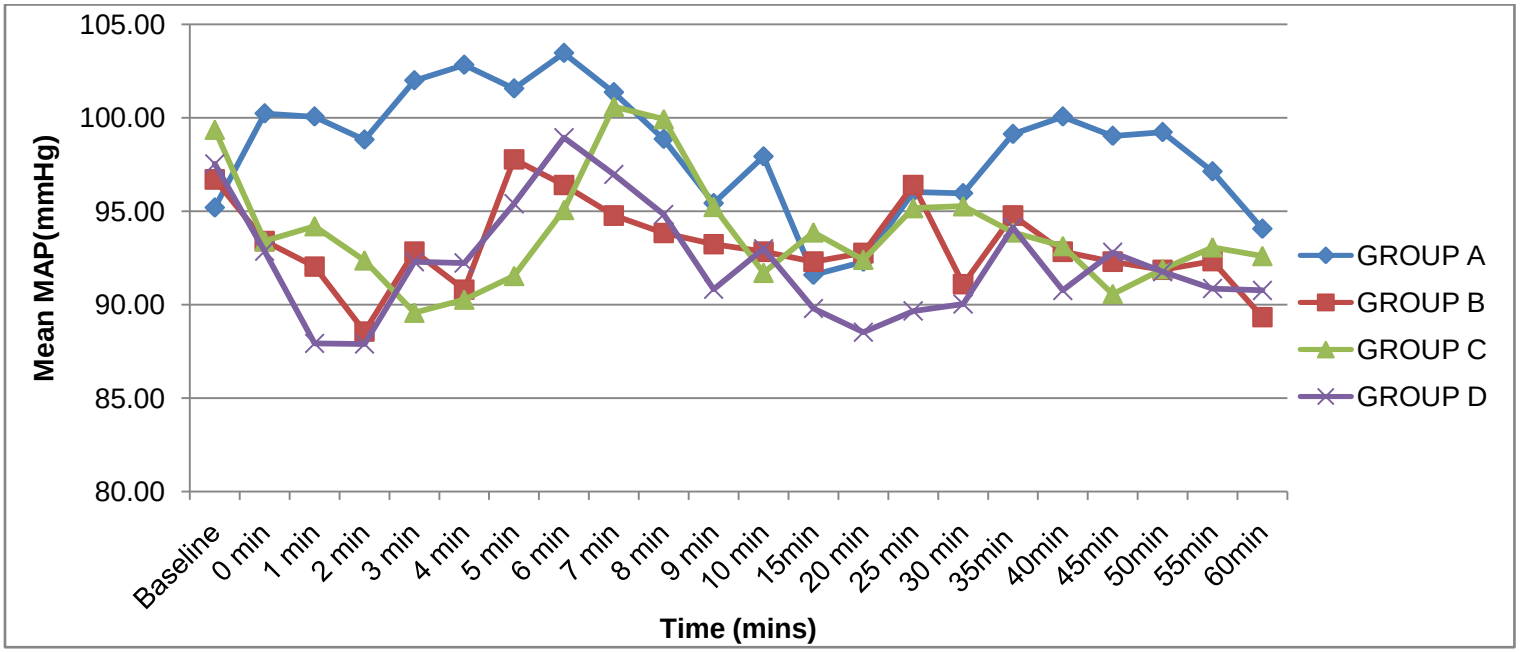


Figure 11: Mean MAP after administration of study drug

Table 12: Mean Percentage variation of MAP from baseline values

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C VS D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
0 min	-6.88	17.21	3.26	12.94	5.84	14.31	4.73	13.55	0.003	0.008	0.001	0.003	0.494	0.697	0.768
1 min	-6.42	16.81	4.00	18.11	4.94	14.62	9.91	16.02	0.002	0.016	0.009	0.000	0.825	0.166	0.244
2 min	-5.63	21.03	7.80	13.63	6.92	15.82	9.69	14.63	0.002	0.002	0.004	0.000	0.838	0.658	0.518
3 min	-8.41	18.63	3.80	18.04	9.64	13.89	5.04	15.45	0.000	0.005	0.000	0.002	0.176	0.773	0.286
4 min	-9.56	21.39	6.00	16.86	9.01	16.62	4.91	16.69	0.001	0.001	0.000	0.002	0.518	0.816	0.380
5 min	-8.44	21.72	-1.25	18.30	7.69	17.76	1.95	21.54	0.020	0.165	0.002	0.046	0.085	0.535	0.267
6 min	-10.52	25.15	0.08	15.78	4.21	14.46	-1.65	20.64	0.032	0.037	0.004	0.080	0.414	0.731	0.246
7 min	-8.71	22.42	1.84	14.08	-1.18	16.91	0.29	15.66	0.100	0.022	0.099	0.049	0.507	0.734	0.746
8 min	-6.06	23.23	2.40	14.58	-0.51	15.17	2.80	17.29	0.202	0.070	0.233	0.058	0.530	0.931	0.475
9 min	-2.35	21.85	3.24	12.88	4.12	11.95	6.71	16.29	0.180	0.185	0.125	0.033	0.833	0.409	0.538
10 min	-4.64	23.99	3.80	13.32	7.56	10.92	4.46	13.29	0.029	0.046	0.004	0.032	0.370	0.875	0.460
15min	2.01	19.22	3.96	17.06	5.25	12.88	7.62	13.86	0.583	0.637	0.433	0.176	0.754	0.376	0.567
20 min	1.38	17.72	3.83	12.54	6.60	14.21	8.74	12.26	0.217	0.510	0.162	0.049	0.456	0.187	0.564
25 min	-2.49	17.65	-0.03	11.42	4.00	12.25	7.97	13.32	0.023	0.492	0.072	0.004	0.263	0.027	0.270
30 min	-2.38	19.14	5.33	12.56	3.91	11.94	7.60	12.59	0.051	0.040	0.093	0.008	0.702	0.542	0.321
35min	-5.77	19.73	1.67	12.61	5.26	11.89	3.26	12.51	0.023	0.050	0.004	0.018	0.341	0.672	0.596
40min	-6.79	19.54	3.64	12.07	5.92	13.07	6.66	10.57	0.001	0.005	0.001	0.000	0.536	0.413	0.841
45min	-5.57	17.05	4.20	13.10	8.73	11.44	4.58	10.76	0.001	0.005	0.000	0.004	0.191	0.913	0.230
50min	-5.59	16.09	4.71	12.38	7.28	10.26	5.46	12.06	0.001	0.002	0.000	0.001	0.441	0.823	0.584
55min	-3.38	18.27	4.23	10.80	6.02	11.83	6.53	11.48	0.018	0.030	0.008	0.005	0.606	0.509	0.884
60min	-0.62	19.73	7.24	12.45	6.55	11.86	6.81	10.58	0.101	0.033	0.052	0.044	0.852	0.907	0.944

The mean percentage increase in MAP was seen in group A. On inter group comparison, this variation was statistically significant when compared with groups B, C and D. But the mean percentage variation of MAP in other groups was statistically insignificant. (Table 12, Figure 12)

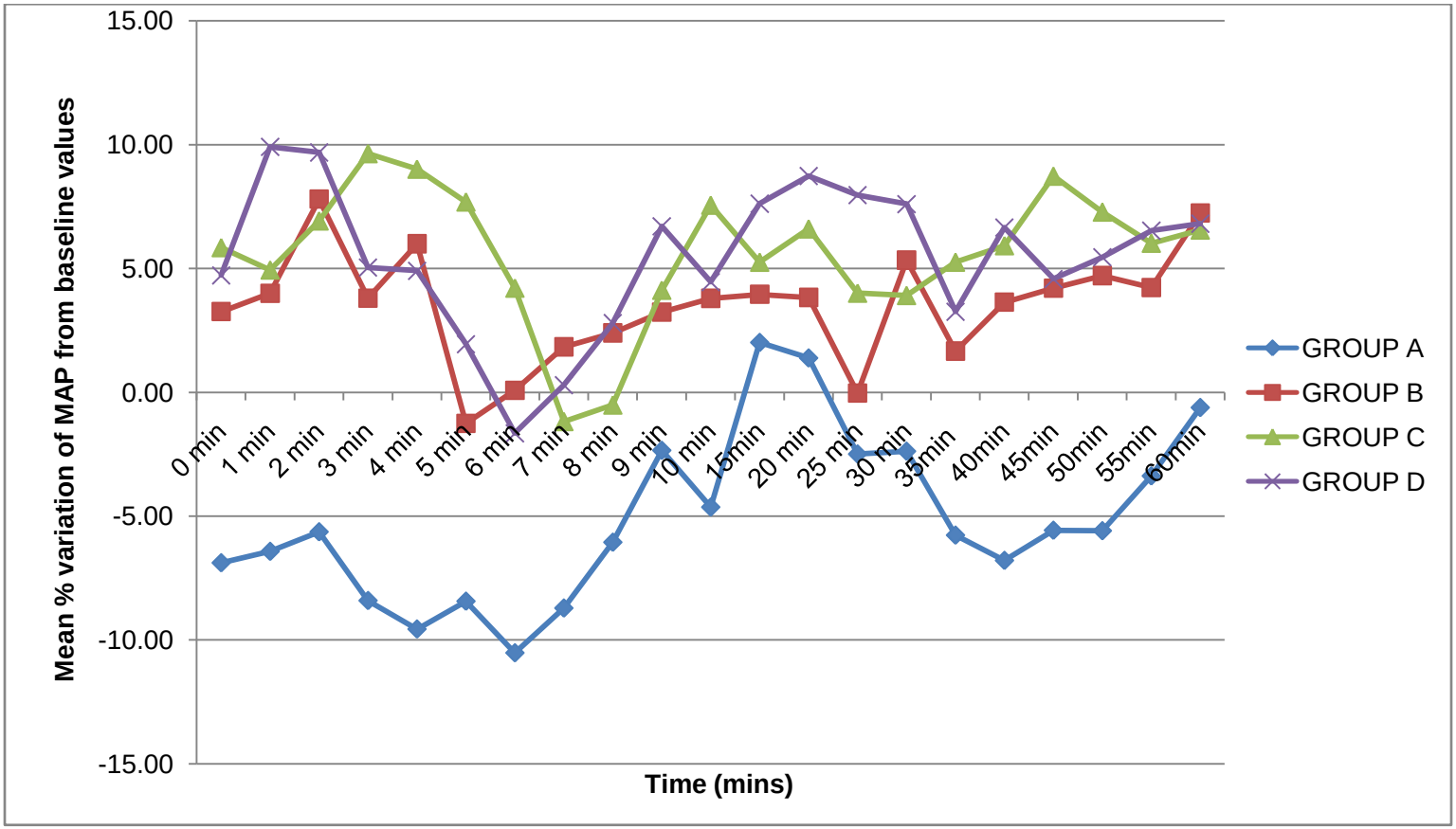


Figure 12: Mean Percentage variation of MAP from baseline values

Table 13: Mean oxygen saturation (SpO_2) after administration of study drug

TIME OF RECORDING (MINS)	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Baseline	98.37	1.13	98.47	1.17	98.43	1.25	98.17	1.18	0.762	0.744	0.827	0.513	0.913	0.328	0.384
0 min	99.03	1.00	99.03	0.81	99.47	0.68	99.07	0.91	0.146	1.000	0.053	0.881	0.053	0.881	0.073
1 min	99.17	0.91	99.13	0.73	99.53	0.63	99.33	0.76	0.166	0.866	0.066	0.400	0.045	0.313	0.313
2 min	99.37	0.76	99.37	0.67	99.70	0.53	99.53	0.78	0.195	1.000	0.065	0.354	0.065	0.354	0.354
3 min	99.60	0.62	99.73	0.58	99.83	0.38	99.73	0.58	0.439	0.350	0.103	0.350	0.483	1.000	0.483
4 min	99.57	0.68	99.83	0.46	99.83	0.38	99.83	0.38	0.090	0.037	0.037	0.037	1.000	1.000	1.000
5 min	99.60	0.67	99.87	0.43	99.83	0.46	99.87	0.35	0.112	0.039	0.070	0.039	0.794	1.000	0.794
6 min	99.63	0.67	99.80	0.55	99.77	0.57	99.80	0.48	0.631	0.261	0.368	0.261	0.822	1.000	0.822
7 min	99.60	0.67	99.73	0.58	99.80	0.48	99.73	0.58	0.606	0.379	0.188	0.379	0.660	1.000	0.660
8 min	99.53	0.78	99.73	0.58	99.70	0.70	99.67	0.61	0.675	0.251	0.338	0.443	0.848	0.701	0.848
9 min	99.57	0.73	99.63	0.61	99.67	0.76	99.60	0.77	0.956	0.721	0.592	0.858	0.858	0.858	0.721
10 min	99.43	0.86	99.60	0.62	99.60	0.81	99.57	0.73	0.806	0.398	0.398	0.499	1.000	0.866	0.866
15min	99.53	0.82	99.53	0.73	99.60	0.77	99.53	0.78	0.983	1.000	0.739	1.000	0.739	1.000	0.739
20 min	99.60	0.77	99.53	0.73	99.53	0.90	99.47	0.82	0.938	0.750	0.750	0.524	1.000	0.750	0.750
25 min	99.60	0.77	99.60	0.62	99.50	0.94	99.50	0.73	0.918	1.000	0.618	0.618	0.618	0.618	1.000
30 min	99.57	0.82	99.60	0.62	99.50	0.94	99.53	0.68	0.964	0.868	0.739	0.868	0.618	0.739	0.868
35min	99.63	0.76	99.63	0.61	99.50	0.94	99.57	0.57	0.878	1.000	0.484	0.726	0.484	0.726	0.726
40min	99.63	0.76	99.70	0.53	99.50	1.01	99.57	0.57	0.752	0.729	0.489	0.729	0.300	0.489	0.729
45min	99.63	0.76	99.70	0.53	99.57	0.86	99.67	0.61	0.898	0.714	0.714	0.855	0.464	0.855	0.583
50min	99.63	0.76	99.70	0.53	99.57	0.77	99.67	0.61	0.888	0.704	0.704	0.849	0.448	0.849	0.569
55min	99.63	0.76	99.70	0.53	99.60	0.67	99.73	0.52	0.841	0.684	0.838	0.541	0.541	0.838	0.416
60min	99.67	0.71	99.70	0.53	99.60	0.67	99.77	0.43	0.751	0.830	0.667	0.519	0.519	0.667	0.283

All the patients had normal mean oxygen saturation at all measurement intervals. The difference of peripheral oxygen saturation between all the four groups was statistically insignificant for the study period (p value >0.05) (Table 13, Figure 13)

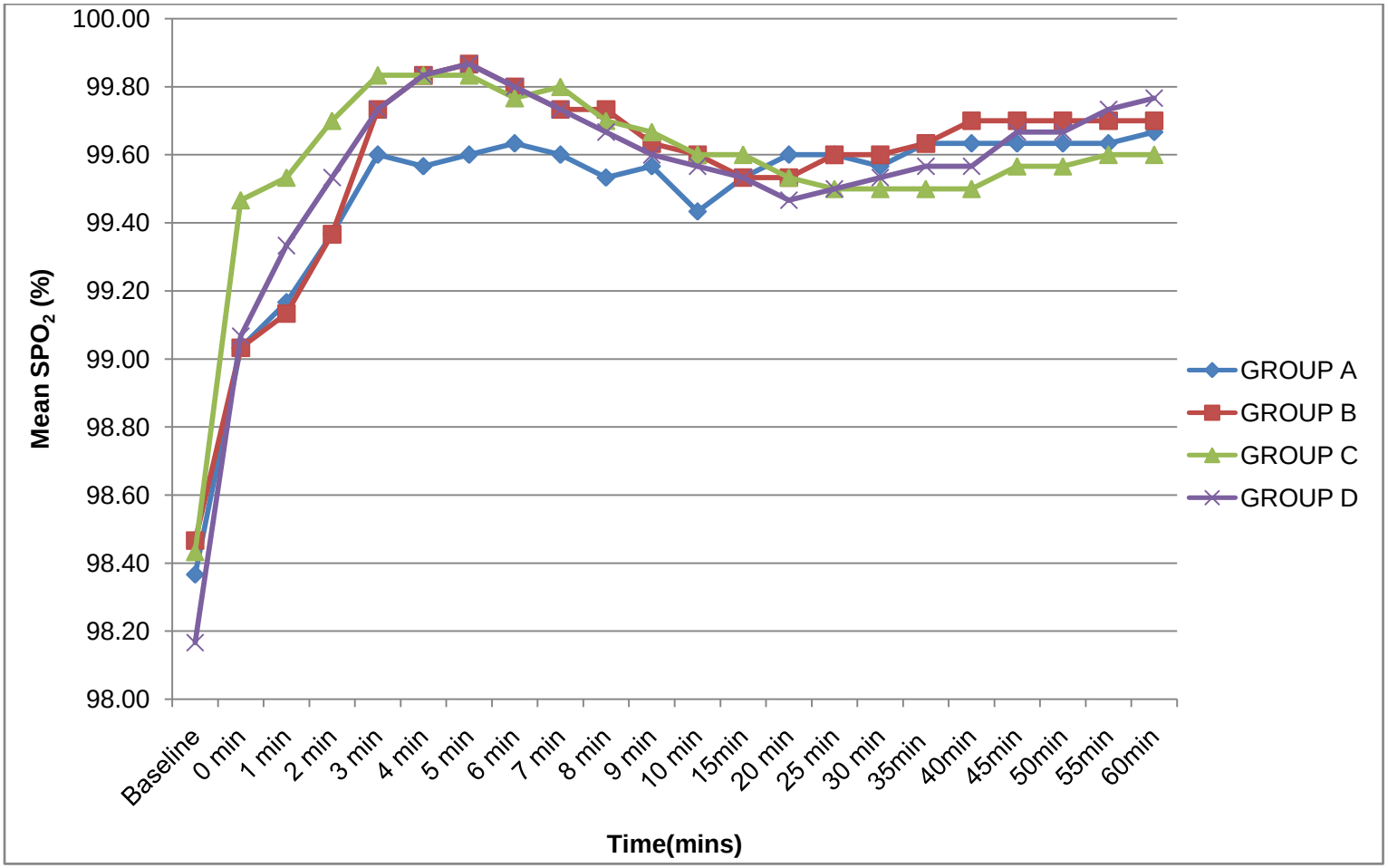


Figure 13: Mean oxygen saturation (SpO_2) after administration of study drug

Table 14: Incidence of myoclonus (0-1 min)

Incidence of myoclonus-0-1min	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
	29	97%	23	77%	13	43%	6	20%	71	0.000	0.023	0.000	0.000	0.008	0.000	0.052

The incidence of myoclonus at 0-1 min was lower in group D (20%) as compared to group B (77%) and group C (43%). On inter group comparison, the incidence was even lower in group C in comparison to group B and this difference was statistically significant (p value <0.05). But the incidence of myoclonus was statistically similar among group C and D. (Table 14, Figure 14)

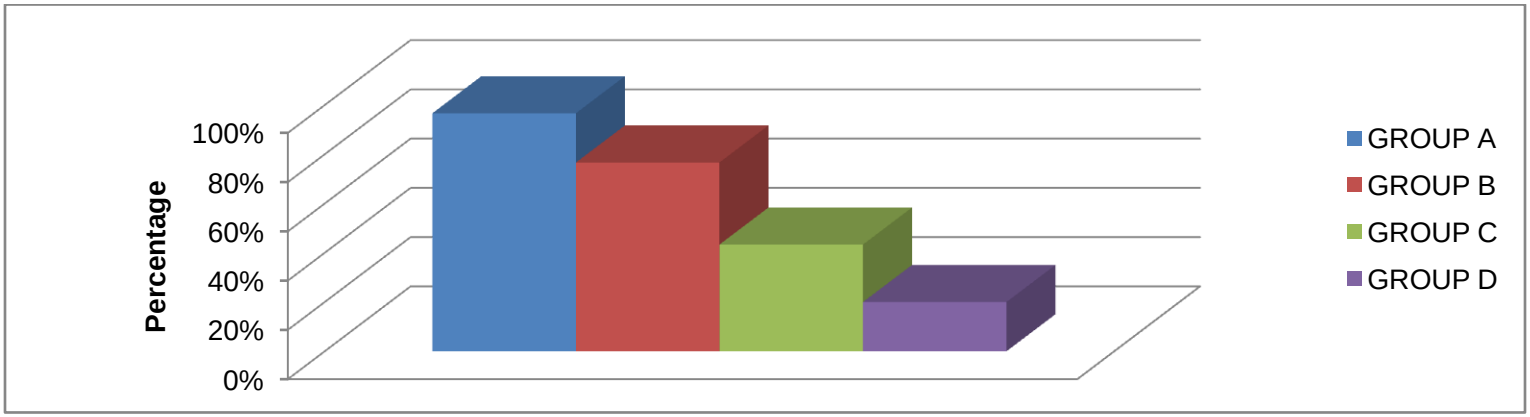


Figure 14: Incidence of myoclonus (0-1 min)

Table 15: Incidence of myoclonus (1-2 min)

Incidence of myoclonus-1-2min	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
	28	93%	26	87%	17	57%	10	33%	81	0.000	0.389	0.001	0.000	0.009	0.000	0.069

The incidence of myoclonus at 1-2 min was lowest in group D (33%) in comparison to group A (93%), group B (87%) and group C (57%). On comparison between the groups B vs C, the incidence was significantly lower in group C. But the incidence of myoclonus was statistically similar among group C and D at 1-2 min also. (Table 15, Figure 15)

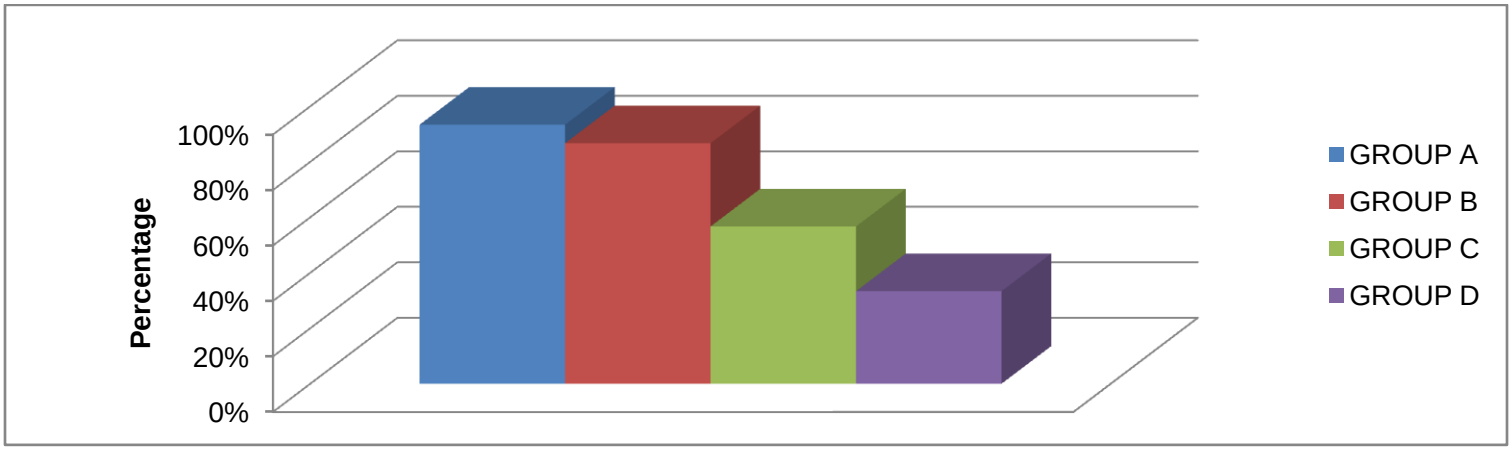


Figure 15: Incidence of myoclonus (1-2 min)

Table 16: Grade of myoclonus (0-1min)

		Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
		GROUP A		GROUPB		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
Grade of myoclonus-0-1min	0	1	3%	7	23%	17	57%	24	80%	49	0.000	0.000	0.000	0.000	0.006	0.000	0.051
	1	3	10%	11	37%	11	37%	3	10%	28							
	2	17	57%	11	37%	1	3%	3	10%	32							
	3	9	30%	1	3%	1	3%	0	0%	11							

The incidence of grade 2 and 3 myoclonus at 0-1 min was more in group A whereas, in other groups the incidence of grade 0 or grade 1 myoclonus was more. On comparison between group B vs C, the incidence of grade 2 myoclonus was lesser in group C. Though, the incidence of grade 3 myoclonus was similar among group B and C. In group D, none of the patients had grade 3 myoclonus and the incidence of grade 1 and 2 myoclonus was similar and lesser than group C. Thus, groups C and D had significantly lesser incidence of grade 3 myoclonus as compared to groups A and B. (Table 16, Figure 16)

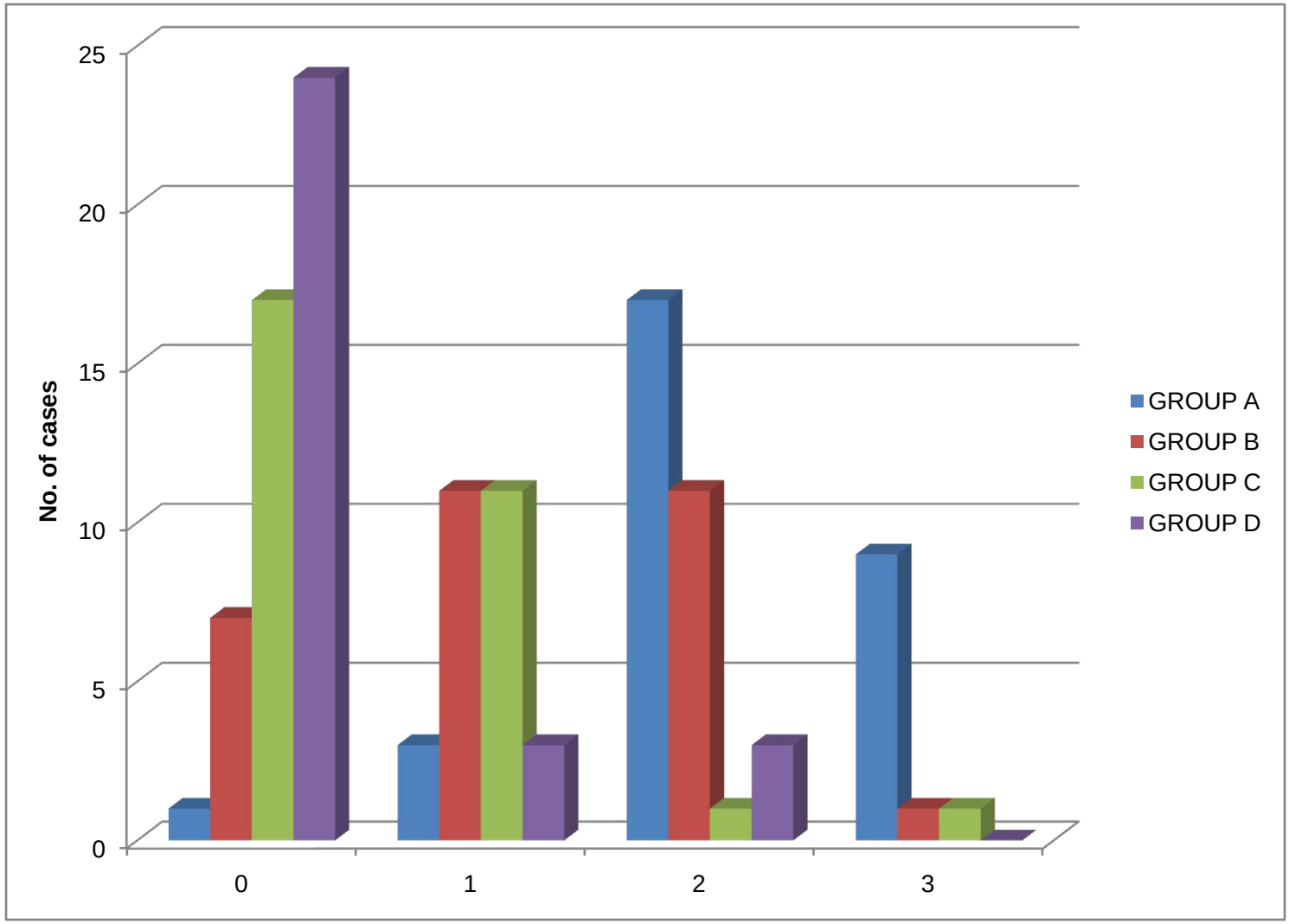


Figure 16: Grade of myoclonus (0-1min)

Table 17: Grade of myoclonus (1-2min)

		Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
		GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
Grade of myoclonus-1-2min	0	2	7%	4	13%	13	43%	20	67%	39	0.000	0.000	0.000	0.000	0.002	0.000	0.192
	1	0	0%	6	20%	9	30%	7	23%	22							
	2	9	30%	20	67%	6	20%	3	10%	38							
	3	19	63%	0	0%	2	7%	0	0%	21							

The incidence of grade 2 and 3 myoclonus at 1-2 min was more in group A and B while in group C and D the incidence of grade 0 or grade 1 was more. On comparison between group B vs C, the incidence of grade 2 myoclonus was lesser in group C. None of the patients had grade 3 myoclonus in group B but 2 patients in group C had grade 3 myoclonus. In group D, none of the patients had grade 3 myoclonus and the incidence of grade 1 and 2 myoclonus was lesser than group C. (Table 17, Figure 17)

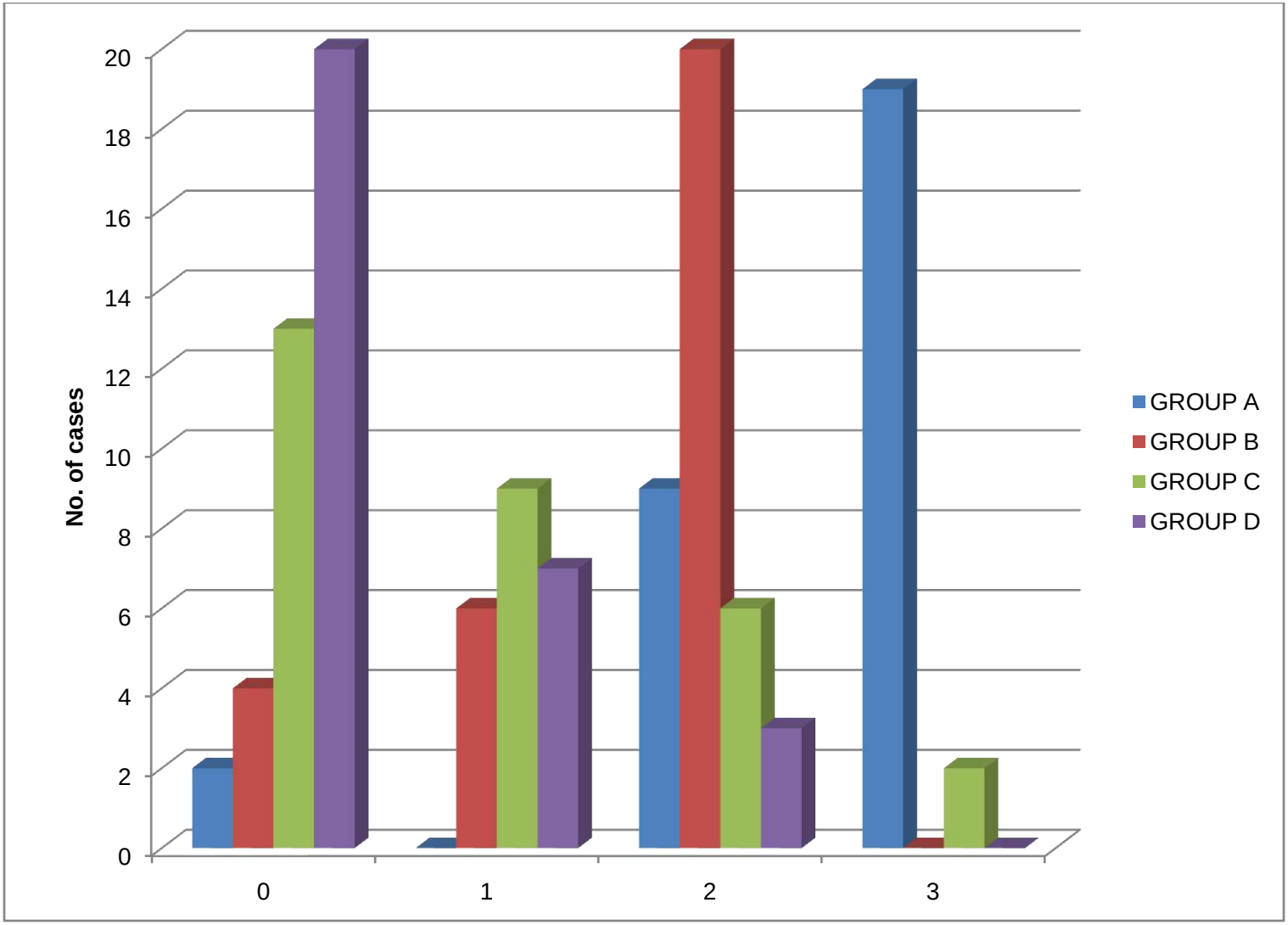


Figure 17: Grade of myoclonus (1-2min)

Table 18: Incidence of adverse effects

ADVERSE EFFECTS	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
Bradycardia	1	3%	0	0%	0	0%	4	13%	5	0.030	0.313	0.313	0.353	1.000	0.112	0.112
Hypotension	1	3%	4	13%	3	10%	14	47%	22	0.000	0.161	0.612	0.000	0.688	0.010	0.003
Tachycardia	9	30%	4	13%	5	17%	2	7%	20	0.101	0.117	0.221	0.019	0.718	0.671	0.424
Hypertension	9	30%	7	23%	4	13%	2	7%	21	0.091	0.559	0.117	0.019	0.506	0.145	0.671

The incidence of bradycardia was highest in group D (13%). However, on inter group comparison, the difference of incidence of bradycardia was statistically not significant.

The incidence of hypotension was highest in group D (47%). On inter group comparison, the incidence of hypotension was statistically similar in group B and C. However, the incidence of hypotension was significantly lower in groups B and C in comparison to group D.

The incidence of tachycardia was highest in group A (30%). However, on inter group comparison, the statistical difference in the incidence of tachycardia was seen only in group A vs D. (p value 0.019)

The incidence of hypertension was highest in group A (30%). However, on inter group comparison, the statistical difference in the incidence of hypertension was seen only in group A vs D. (p value 0.019) (Table 18, Figure 18)

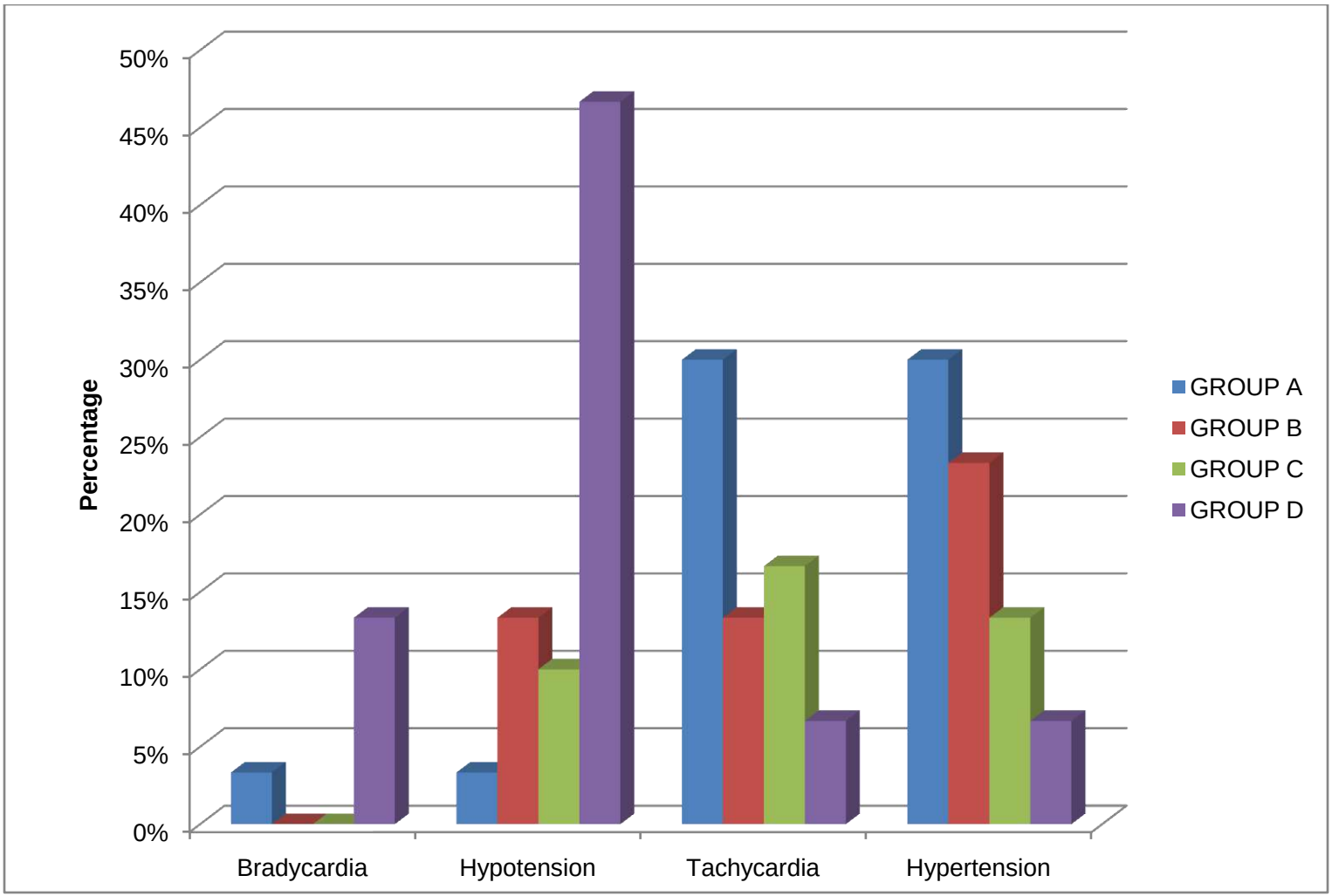


Figure 18: Incidence of adverse effects

Table 19: Mean no. of cases in which atropine bolus given

No. of cases receiving atropine bolus	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
	1	3%	0	0%	0	0%	4	13%	5	0.030	0.313	0.313	0.353	1.000	0.112	0.112

The mean no. of cases in which atropine bolus given were higher in group D 4(13%) as compared to group A 1(3%). But on inter group comparison, the difference was statistically not significant. (Table 19, Figure 19)

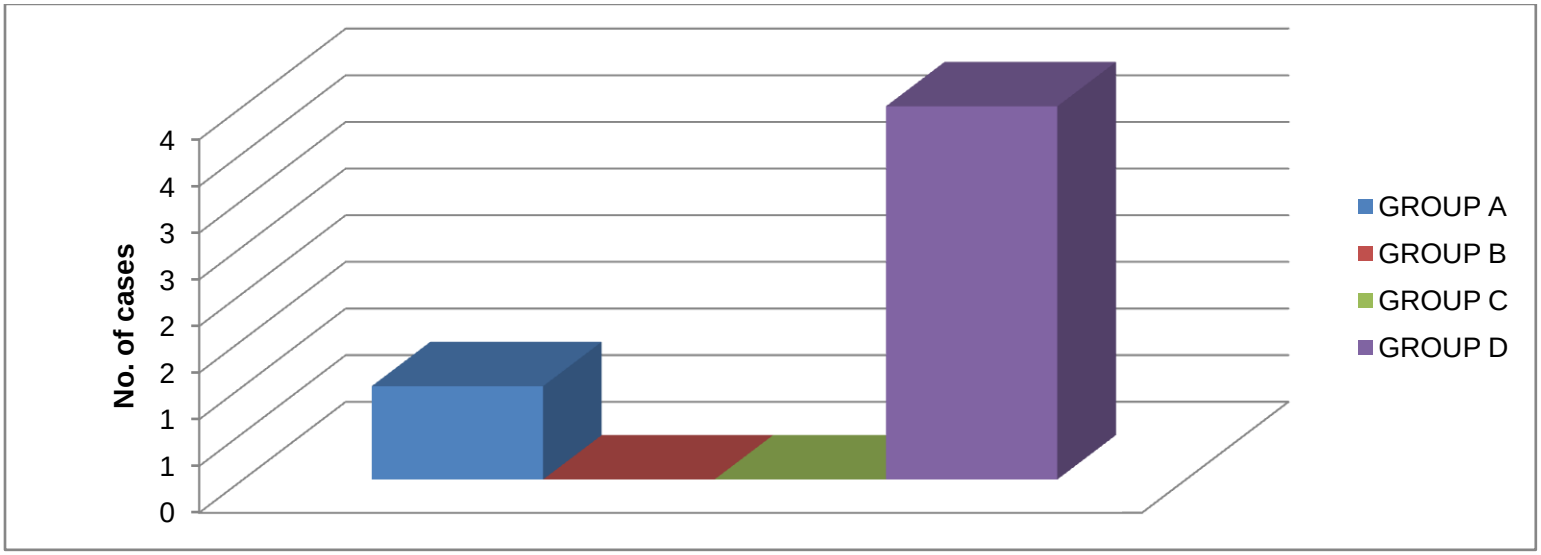


Figure 19: Mean no. of cases in which atropine bolus given

Table 20: Mean dose of atropine bolus given

	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
Mean dose of atropine bolus given(mg)	0.02	0.11	0.00	0.00	0.00	0.00	0.10	0.28	0.031	0.604	0.604	0.040	1.000	0.010	0.010

The mean dose of atropine bolus administered was significantly higher in group D 0.10±0.28 mg as compared to group A 0.02±0.11 mg. No dose of atropine was given in group B and C. (Table 20, Figure 20)

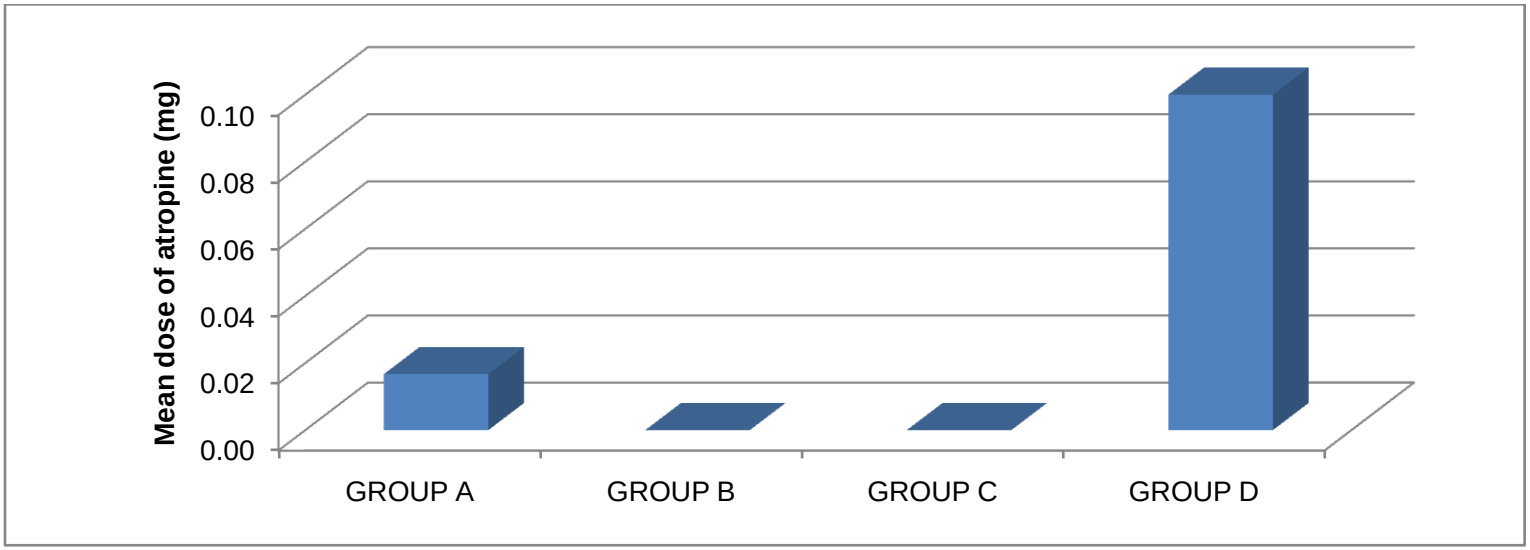


Figure 20: Mean dose of atropine bolus given

Table 21: Mean no. of cases in which ephedrine bolus given

No. of cases receiving ephedrine bolus	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
	1	3%	4	13%	3	10%	14	47%	22	0.000	0.161	0.612	0.000	0.688	0.010	0.003

The mean no. of cases in which ephedrine bolus given were significantly higher in group D 14(47%) as compared to group A 1(3%), group B 4(13%) and group C 3(10%). On inter group comparison, no significant difference was seen in group B vs C. (Table 21, Figure 21)

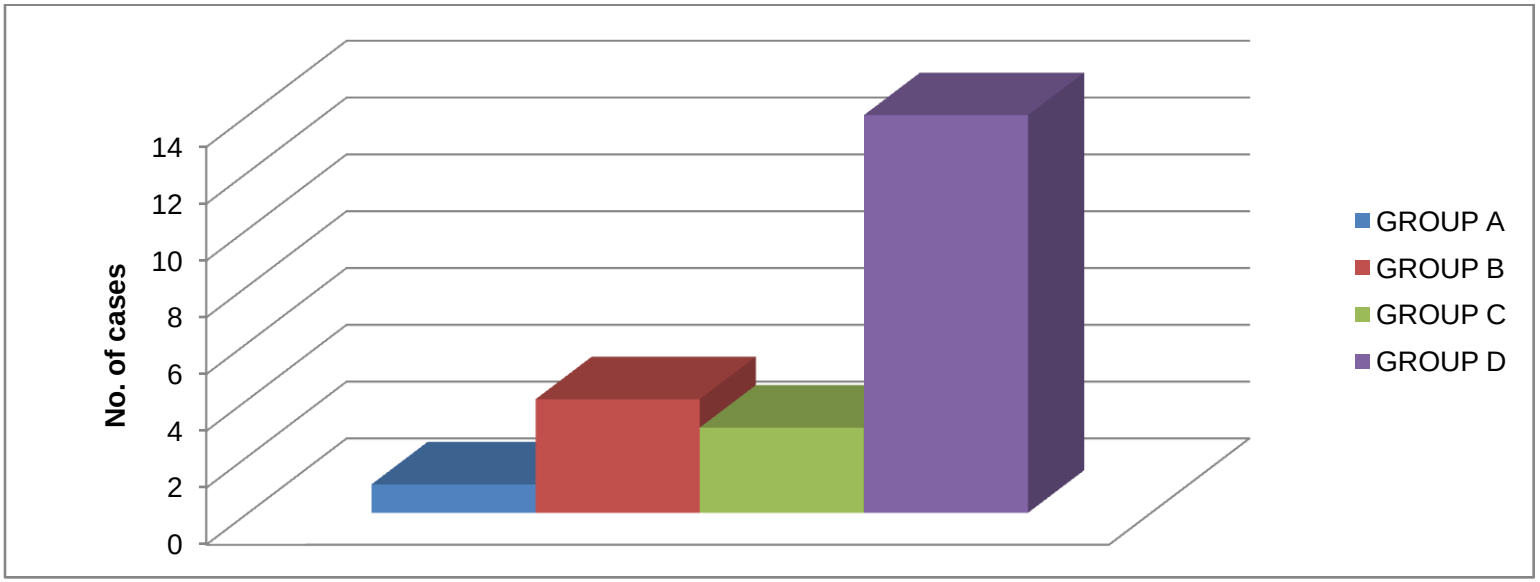


Figure 21: Mean no. of cases in which ephedrine bolus given

Table 22: Mean dose of Ephedrine bolus given

	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Mean dose of ephedrine bolus given (mg)	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
	0.20	1.10	1.60	4.44	1.00	3.55	5.40	8.09	0.000	0.278	0.535	0.000	0.641	0.004	0.001

The mean dose of ephedrine bolus administered was significantly higher in group D 5.40±8.09 mg as compared to other groups. No statistically significant difference was observed in group B and C. (Table 22, Figure 22)

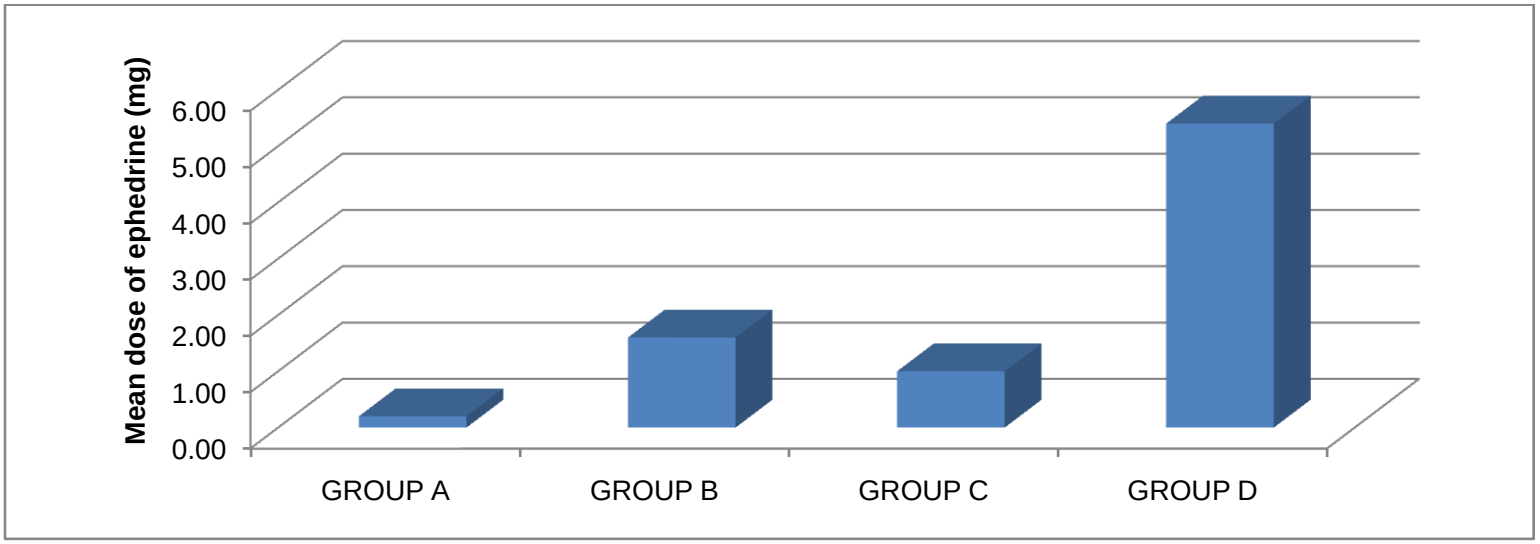


Figure 22: Mean dose of Ephedrine bolus given

Table 23: Mean no. of cases in which Fentanyl bolus given

No. of cases receiving fentanyl bolus	Group								Total	p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
	GROUP A		GROUP B		GROUP C		GROUP D				p-value	p-value	p-value	p-value	p-value	p-value
	10	33%	7	23%	5	17%	2	7%	24	0.069	0.390	0.136	0.021	0.519	0.145	0.424

The mean no. of cases in which fentanyl bolus given to suppress the pressor response were significantly higher in group A 10(33%) as compared to group D 2(7%). On inter group comparison, no significant difference was seen in group B vs C (Table 23, Figure 23)

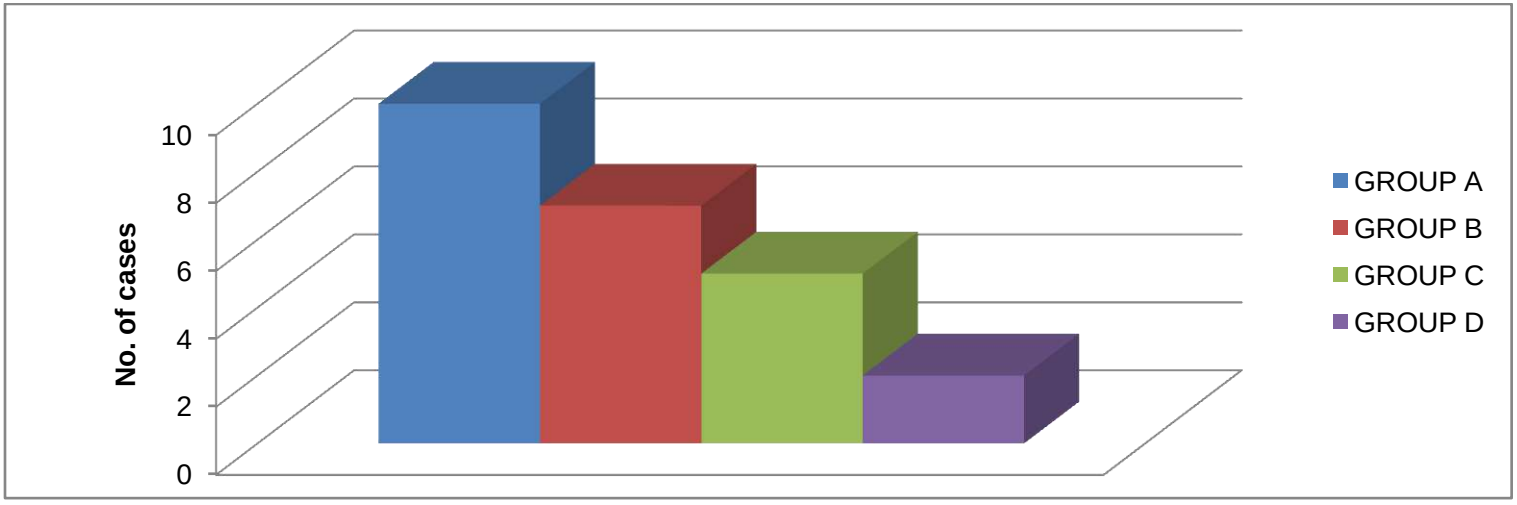


Figure 23: Mean no. of cases in which Fentanyl bolus given

Table 24: Mean dose of Fentanyl given

	GROUP A		GROUP B		GROUP C		GROUP D		p-value	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Mean dose of fentanyl bolus given (ug)	Mean	SD	Mean	SD	Mean	SD	Mean	SD		p-value	p-value	p-value	p-value	p-value	p-value
	29.00	45.81	16.33	30.23	11.67	26.66	4.00	15.45	0.022	0.122	0.035	0.003	0.567	0.132	0.347

The mean dose of fentanyl bolus administered to suppress the pressor response was significantly higher in group A 29.00±45.81 µg as compared to group D 4.00±15.45 µg and group C 11.67±26.66. No significant difference was seen in group B vs C. (Table 24, Figure 24)

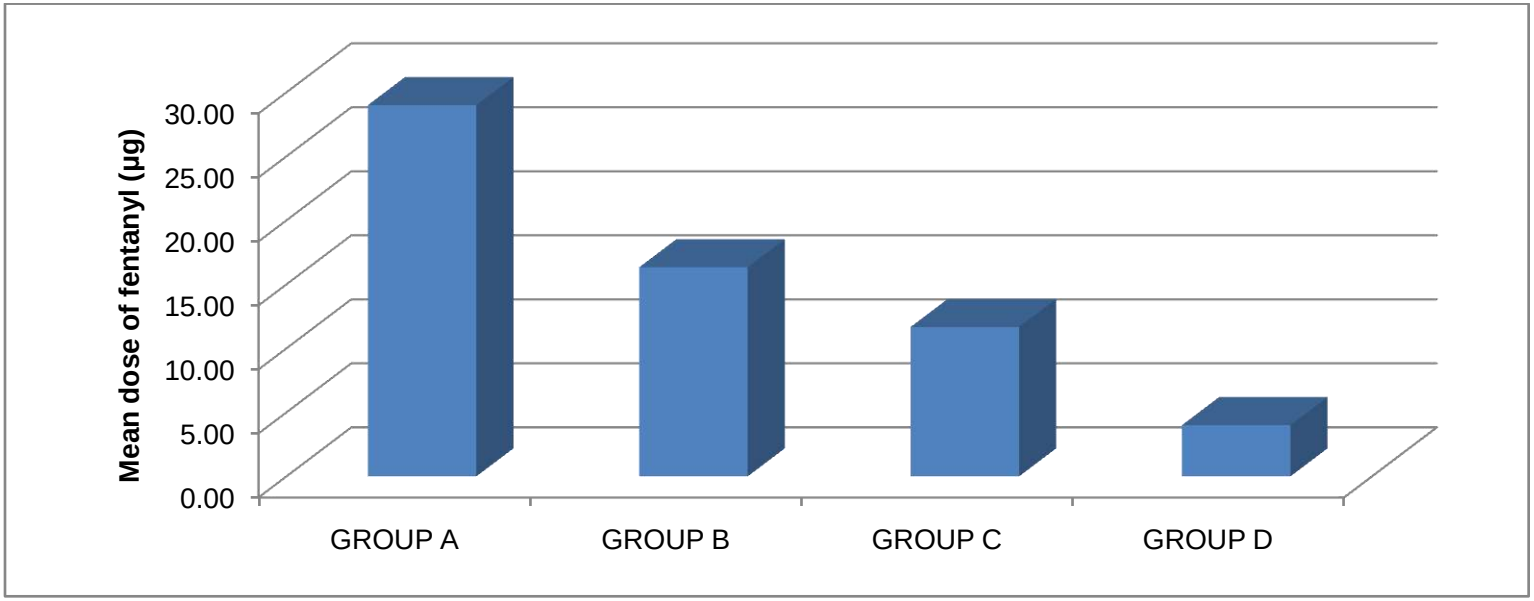


Figure 24: Mean dose of Fentanyl given

DISCUSSION

Etomidate is an attractive induction agent due to its several desirable properties such as rapid onset, brevity of action and lack of cardiovascular depression. However, its use is associated with adverse effects like myoclonus which can result in various complications. The use of etomidate was found to be associated with higher incidence of myoclonic activity upto 70-80% in non premedicated patients.[3,5-8] Keeping in mind the potential complications of myoclonus, a preventive approach is preferable. It is important to blunt these undesirable movements by choosing an optimal agent as premedication, taking into account the type and duration of surgery and patient's condition.

Dexmedetomidine has been used to prevent myoclonus and it has shown promise in reducing the incidence of etomidate induced myoclonus, with the advantage that respiratory depression is avoided.[57] However, the ideal dose which prevents myoclonus with least possible adverse effects is still not known. Few trials have evaluated 0.5 μg kg^{-1} and 1 μg kg^{-1} for prevention of etomidate induced myoclonus and reported it to be effective. Kundra et al[38] used the dose of 0.25 μg kg^{-1} for cessation of post spinal shivering and Ramaswamy et al[64] for sedation in vitreoretinal surgery under peribulbar anaesthesia. They found this dose to be superior as compared to higher doses, as this dose is associated with very less adverse effects. The present study, therefore, was planned to compare the effects of three different dexmedetomidine doses of 0.25 μg kg^{-1}, 0.5 μg kg^{-1} and 1 μg kg^{-1} for prevention of etomidate induced myoclonus and to find a minimum effective dose while avoiding adverse effects associated with its use.

In our study, the patients were randomly divided into four groups of 30 patients each. In group A, 10 ml of isotonic saline was administered. In group B, C and D dexmedetomidine 0.25 μg kg^{-1} , 0.5 μg kg^{-1} and 1 μg kg^{-1}

diluted with isotonic saline to make a final volume of 10 ml was administered over 10 min respectively.

No patient was excluded and all the enrolled patients completed the study. The patients in all the groups were comparable with respect to age, gender, weight, height and ASA physical status. This is important because these demographic factors have the potential to influence the incidence and severity of myoclonus. Luan et al[7] and Dixit et al[2] had also previously studied the effect of dexmedetomidine for prevention of etomidate induced myoclonus using a similar demographic profile. They found it adequate to study the incidence and severity of myoclonus.

The anaesthetic technique was standardized in all the study groups. The hemodynamic parameters-HR and blood pressures (SBP, DBP and MAP) were noted at baseline, after completion of infusion of study drug (i.e. time '0') and every 1 minute for initial 10 minutes and then every 5 minutes till the end of 60 minutes. Incidence of myoclonus, grade of myoclonus, adverse effects, number of bolus and dose given for treatment of adverse effects were also noted.

HR RESPONSE

In our study, the mean baseline heart rate was comparable among all the four groups. We noted a fall of HR immediately after completion of dexemedetomidine infusion in group B, C and D in comparison to baseline. This can be explained by the mechanism of dexmedetomidine whereby it act on α2A-AR receptors and decreases central sympathetic outflow.[57] The fall was greatest in group D (1 μg kg^{-1}) as compared to group B and C. Our findings are in concordance with the study conducted by Menda et al, who demonstrated that dexmedetomidine as an adjunct to anaesthetic induction to attenuate hemodynamic response to endotracheal intubation leads to suppression of heart rate, when dexmedetomidine was used in a dose of 1 μg kg^{-1}.[65]

In our study, the mean HR remained below the baseline in groups B, C and D at most time intervals whereas in group A, it was near the baseline. The mean HR was found to be lowest in group D. Keshri et al compared the effect of 0.5 μg kg^{-1} and 1 μg kg^{-1} dexmedetomidine on hemodynamic response during laryngoscopy and endotracheal intubation in spine surgeries. They observed a decrease in HR below the baseline at all the time intervals in both the study groups in comparison to the normal saline group.[66]

According to the study conducted by Thomas et al, dexmedetomidine led to decrease in HR in a dose dependant manner.[67] The present study reported similar findings, as HR was found to be lowest in group D followed by group C and B.

In our study, no significant difference was found in mean heart rate values between group C vs D. On the other hand, the study conducted by Gupta et al[37] and Keshri et al[66] to study the effect of Dexmedetomidine to attenuate the adverse hemodynamic responses of direct laryngoscopy and intubation showed significant decrease in HR in 1 μg kg^{-1} pretreatment group in comparison to 0.5 μg kg^{-1} group.

Ghaffar et al found no significant difference in mean HR values in dexmedetomidine 0.2, 0.3 and 0.5 μg kg^{-1} treated groups, while studying safety and efficacy of these doses of dexmedetomidine in treating post spinal anaesthesia shivering.[68] Our findings are also comparable with the results of this study, as mean HR values were similar among group B and C at all time intervals during the study period.

PRESSOR RESPONSE

In our study, the mean baseline BP (SBP, DBP, MAP) of the patients showed no statistically significant difference in all the four groups. We observed that there was a suppression of the mean baseline BP immediately after infusion of dexmedetomidine in all the groups except in normal saline group. This was expected, as hypotension occurs after dexmedetomidine due to decreased sympathetic outflow.[57] The mean BP

(SBP, DBP, MAP) values were lowest in group D. Our findings are in concordance with the study done by Keshri et al to attenuate the hemodynamic responses of direct laryngoscopy and intubation. The mean BP was significantly lower in 1 μg kg^{-1} dexmedetomidine group than normal saline group at all the times during study period.[66]

In our study, no significant difference was found among groups C and D. On the other hand, Gupta et al[37] and Keshri et al[66] found significantly lower BP in dexmedetomidine 1 μg kg^{-1} treated group than 0.5 μg kg^{-1} treated group in their study.

The mean BP values were comparable between dexmedetomidine 0.5 μg kg^{-1} and 0.25 μg kg^{-1} treated groups in our study. On the other hand, Ramaswamy et al and Aho et al found lower BP readings in 0.5 μg kg^{-1} treated group in comparison to lower doses. This could be due to the difference in health status and adequate intravascular volume status in our patients prior to anaesthesia.

INCIDENCE OF MYOCLONUS

Dexmedetomidine has been reported to reduce the incidence of myoclonus in a dose dependent manner. We also noted a highly significant reduction in the incidence of myoclonus in dexmedetomidine treated groups as compared to the normal saline group. The incidence was reduced by 77% in group D in comparison to the normal saline group. Our findings are supported by Dixit et al[2] and Aktolga et al[69], who also reported the significant reduction in the incidence of myoclonus in dexmedetomidine (1 μg kg^{-1}) treated group as compared to normal saline following etomidate injection.

Miao et al[70] and Mizrak et al[33] established that administering 0.5 μg kg^{-1} dexmedetomidine prior to etomidate induction dose lead to significant reduction in the incidence of myoclonus in comparison to normal saline group. Findings of our study suggested that dexmedetomidine in a dose of 0.5 μg kg^{-1} is equally effective in reducing the incidence of myoclonus as 1 μg kg^{-1} dose. Similar findings have also been reported by Luan et al who

showed that the incidence of myoclonus after etomidate was reduced in patients treated with dexmedetomidine in comparison to isotonic saline group. But no significant difference was seen between 0.5 μg kg^{-1} and 1 μg kg^{-1} groups.[7]

Further, we observed that dexmedetomidine in a dose of 0.25 μg kg^{-1} was effective in prevention of myoclonus but significantly lesser than 0.5 μg kg^{-1} and 1 μg kg^{-1} dose. There is no study in the literature, in which 0.25 μg kg^{-1} dexmedetomidine has been used to prevent the myoclonus induced by etomidate.

GRADE OF MYOCLONUS

The incidence and grades of myoclonus were lesser in group C and D, while in group A, the incidence of myoclonus was highest and patients had severe grades (grade 2 and 3) of myoclonus. Our findings are in concordance with Dixit et al who reported that placebo group had experienced more severe myoclonus (grade 2 and 3) while the dexmedetomidine 1 μg kg^{-1} group had more of myoclonus of grade 1.[2] Another study conducted by Aktolga et al also reported similar findings.[69] Similar findings were reported by studies conducted by Miao et al[70] and Mizrak et al[33] who had compared 0.5 μg kg^{-1} dexmedetomidine with placebo group to find the incidence and severity of myoclonus. They had observed lesser incidence and severity of myoclonus in dexmedetomidine (0.5 μg kg^{-1}) treated groups in comparison to placebo group.

In our study, we observed that no patient in group D had severe myoclonus (grade 3). Our findings are comparable to a study by Luan et al[7] and Altolga et al[69] who also noted that no patient in dexmedetomidine (1 μg kg^{-1}) treated group had grade 3 myoclonus.

Further, we found that severity of myoclonus in group C was lesser than group B in our study. There is no study in the literature in which dexmedetomidine 0.25 μg kg^{-1} dose has been used to prevent the myoclonus.

ADVERSE EFFECTS OBSERVED AND TREATMENT RECEIVED

In our study, 4 out of 30 patients had bradycardia in group D and 1 out of 30 patients in group A. For each episode of bradycardia 0.6 mg IV Atropine was administered. In group B and C, none of the patients had bradycardia. On intergroup comparison, the difference in the incidence of bradycardia was not significant among all the four groups.

Findings similar to our study have also been reported by Dixit et al[2] and Miao et al[70] who found no significant difference in the incidence of bradycardia among dexmedetomidine treated group and normal saline group.

In our study, the incidence of bradycardia was comparable among groups C and D. On the other hand, Luan et al found significantly greater incidence of bradycardia in dexmedetomidine (1 μg kg^{-1}) treated group in comparison to dexmedetomidine (0.5 μg kg^{-1}) and normal saline group.[7]

The incidence of hypotension was highest in group D (47%), in our study. The incidence of hypotension was significantly lower in group B and C in comparison to group D. Findings similar to our study has been reported by Jamal et al[71] and Kundra et al[38] who found that dexmedetomidine in a dose of 1 μg kg^{-1} causes significant hypotension in comparison to 0.5 μg kg^{-1} and 0.25 μg kg^{-1} dose. However, the incidence of hypotension was similar in group B and C in our study. On the other hand, the study conducted by Ramaswamy et al to evaluate the effect of dexmedetomidine 0.25 and 0.5 μg kg^{-1} in vitreoretinal surgery concluded that 0.5 μg kg^{-1} dose causes significant hypotension than 0.25 μg kg^{-1} dose.[64] Similar findings has been reported by Ghaffer et al while studying safety and efficacy of dexmedetomidine in treating post spinal anaesthesia shivering.[68]

In our study, the incidence of tachycardia and hypertension was significantly higher in group A as compared to group D. But there was no significant difference between group B and C. This could be due to the higher incidence and severity of myoclonus in group A, as it has been

found that myoclonus is associated with post induction tachycardia and hypertension. Rescue treatment given in the form of fentanyl bolus was also found to be highest in group A and no significant difference was found in group B and C. Our findings are in concordance with the study done by Prakash et al who showed that myoclonus is associated with a higher post induction hemodynamic variations.[9]

There are certain limitations of study which are worth mentioning. First of all, the study was conducted on healthy ASA I and II patients, while etomidate is often administred as an induction agent in hemodynamically unstable patients. Thus, dose related adverse effects of dexmedetomidine for prevention of etomidate induced myoclonus on such hemodynamically unstable patients could not be evaluated.

Secondly, etomidate is known to cause adrenal suppression and this aspect of etomidate induced adverse effect was also not be studied.

Thirdly, fluid administration was at the discretion of attending anesthesiologist and was not standardized in all the groups. Hydration status of patient can potentially affect dexmedetomidine induced changes in heart rate and blood pressure, as dexmedetomidine is known to cause more pronounced hypotension and bradycardia in hypovolemic patients.[72] This might be a potentially confounding factor. However, we believe that randomization and blinding of the attending anesthesiologist would have taken care of this factor.

SUMMARY AND CONCLUSION

The present study was conducted in the Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana after approval from institutional Ethics Committee. One hundred and twenty ASA I and II patients, between 18 to 60 years of age, posted for elective surgery under general anaesthesia were enrolled for this prospective, double blind, randomized controlled trial. The patients were randomly divided into four groups of 30 patients each.

The anaesthetic technique was standardized in all the study groups. In group A patients 10 ml of isotonic saline was given. In group B patients were given dexmedetomidine 0.25 µg kg^{-1}, in group C dexmedetomidine 0.5 µg kg^{-1}, in group D dexmedetomidine 1 µg kg^{-1} diluted with isotonic saline to make a final volume of 10 ml which was administered over 10 min. Once the infusion was completed, this time was labelled as '0' and 0.3 mg kg^{-1} etomidate was injected intravenously over a period of 30 sec. Patients were observed continuously for myoclonus for 2 min. Measurements including heart rate (HR), systolic blood pressure (SBP), Diastolic blood pressure (DBP) and mean arterial pressure (MAP) were made at the following time intervals: Before administering the study drug (Baseline), just after completion of infusion of study drug (i.e. time '0') and every 1 minute for initial 10 minutes and then every 5 minutes till the end of 60 minutes. Incidence of myoconus, grade of myoclonus, adverse effects, no. of bolus and dose given for treatment of adverse effects were also recorded.

The following conclusions were drawn during the study period:

- The patients in all the groups were comparable with respect to age, gender, weight, height and ASA physical status.
- The mean HR values after administration of study drug were lowest in group D and comparable among group B and C.

- The mean percentage increase in HR after administration of study drug (from baseline values) was highest in group A.
- The mean BP (SBP, DBP, MAP) values after administration of study drug remained below the baseline in group B, C and D at most time intervals. The mean BP was found to be lowest in group D but no significant difference was found when group C and D, group B and C were compared.
- The mean percentage rise of MAP after administration of study drug (from baseline values) was significantly higher in group A in comparison to group B, C and D.
- The incidence of myoclonus was significantly lesser in dexmedetomidine treated groups as compared to normal saline group. The incidence was comparable among group C and D whereas it was found to be significantly higher in group B in comparison to group C and D.
- Patients in group A had more severe grades (grade 2-3) of myoclonus compared to dexmedetomidine treated groups. No patient in group D had severe myoclonus. Severity of myoclonus was lesser in group C as compared to group B.
- The incidence of bradycardia and hypotension was highest in group D. The incidence of hypotension was significantly lower in group B and C in comparison to group D. However, the incidence of hypotension was similar among group B and C.
- The incidence of tachycardia and hypertension was significantly higher in group A as compared to group D. But it was comparable among other groups. Rescue treatment used in the form of fentanyl bolus were also found to be highest in group A and no significant difference was found in group B and C.

Hence, we conclude that all the three doses of dexmedetomidine are effective in reducing the incidence and severity of myoclonus. A loading

dose of dexmedetomidine 0.5 μg kg^{-1} over 10 min before etomidate injection is the most effective dose with minimum side effects.

In accordance to our findings, dexmedetomidine 0.5 μg kg^{-1} loading dose can be safely used before etomidate induction for prevention of etomidate induced myoclonus.

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DEPARTMENT OF ANAESTHESIOLOGY

DAYANAND MEDICAL COLLEGE AND HOSPITAL, LUDHIANA

PROFORMA

MRD No.	**DOA**	**DOD**
Admission No.	**Diagnosis**	**Randomization number**
Age	**Sex**	**ASA Grading**
Height	**Weight**	**BMI**
GPE: (Date) **P C J E LAP**	**Systemic Exam: (+** **finding Only)** **Chest** **CVS** **Abdomen**	**CNS Examination:**
Surgery start: Date/time	**Anaesthesia start:** **Date/time**	**H/o drug allergy**
Surgery finish: Date/time	**Anaesthesia finish: Date/** **time**	**H/o steroid intake**

Signature of Candidate **Signature of Supervisor**

BASELINE VITALS:

HR:	**SBP:**
RR:	**DBP:**
SPO_2:	**MAP:**

GRADE OF MYOCLONUS:

Time	**1min**	**1-2 min**
Grade		

Signature of Candidate **Signature of Supervisor**

INTRAOPERATIVE MONITORING:

Time in mins.

VITALS	0	1	2	3	4	5	6	7	8	9	10	15	20	25	30	35	40	45	50	55	60
HR																					
NIBP (mmHg) Systolic																					
Diastolic																					
Mean																					
SpO_2																					

Signature of Candidate **Signature of Supervisor**

ADVERSE EFFECTS:

Observed during initial 60 mins after drug administration	Number of episodes	Treatment given	Dose of drug administered
Bradycardia (HR<50/min)			
Hypotension (SBP<90mmHg or DBP<60mmHg)			
Tachycardia (HR> 20% of baseline value)			
Hypertension (blood pressure > 20% of baseline value			

Signature of Candidate **Signature of Supervisor**

									Anaesthesia Start		Surgery Start	Surgery Finish	Anaesthesia finish	Duration	BASELINE VITALS						GRADE OF MYOCLONUS		HR(Per min)															
																					Grade																	
Sr. No	Group	MRD No	Age(yrs)	Sex	ASA Grading	Height(ft and inches)	Weight (kg)	BMI	Date	Time	Time	Time	Time	Time	HR(bpm)	RR (per min)	SPO2(%)	SBP(mmhg)	DBP(mmhg)	MAP (mmhg)	0-1min	1-2 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min
1	A	530507	27	M	I	5'10"	54	17.64	17/12/18	9:22 AM	9:45 AM	2:35PM	2:45PM	5:23	106	16	99	122	75	92	3	3	99	100	90	103	100	76	80	124	112	103	88	74	70
2	D	636731	33	M	II	5'8"	64	22.14	18/12/18	9:30 AM	10AM	12:15PM	12:30PM	3	100	16	98	138	91	108	2	2	85	86	91	84	88	98	109	111	166	144	134	114	116
3	D	498498	40	M	II	6'	84	25.92	18/12/18	12:45 PM	1:20PM	3:15PM	3:30PM	2:45	96	16	100	135	89	107	0	0	80	71	64	86	83	91	92	82	89	83	85	86	85
4	A	640208	33	M	I	5'9"	90	30	20/12/18	12:10PM	12:30PM	1:15PM	1:30PM	1:20	74	16	97	135	83	100	1	0	77	68	76	94	84	66	98	92	72	70	61	63	66
5	D	637747	43	F	I	5'1"	50	21.64	20/12/18	1:10 PM	1:40PM	4PM	4:15PM	3:05	95	16	98	138	69	96	0	0	75	61	62	94	103	130	88	73	64	66	78	81	84
6	C	638859	34	F	I	5'3"	72	29.26	21/12/18	9:45AM	10:10AM	11:15AM	11:30AM	1:45	78	16	99	115	76	95	0	0	59	61	73	75	111	100	114	99	106	90	86	81	84
7	B	704418	32	M	I	5'6"	70	25.73	3/1/2019	1:20PM	2:10PM	3:10PM	3:30PM	1:50	76	16	98	136	80	96	2	2	66	68	72	78	86	72	74	74	76	72	72	74	78
8	D	647802	42	M	II	5'8"	56	19.37	4/1/2019	1PM	1:25PM	2:45PM	3:10PM	2:10	66	18	97	115	78	91	2	2	58	60	67	81	84	64	81	79	64	60	60	56	59
9	B	339375	18	F	I	5'2"	50	20.83	5/1/2019	12:45PM	1PM	1:45PM	2PM	1:15	128	14	100	135	75	97	1	0	114	102	99	101	93	116	122	118	118	102	98	92	95
10	C	654177	40	M	I	5'9"	83	28.13	7/1/2019	10AM	10:30AM	12:15PM	12:30PM	2:30	92	16	96	138	67	100	0	0	79	69	70	69	88	94	111	94	108	102	97	95	100
11	C	149379	32	F	II	5'3"	72	29.26	4/4/2019	2PM	2:30PM	3:25PM	3:30PM	1:30	83	16	99	132	89	108	0	2	66	62	70	73	68	65	65	78	82	89	83	74	70
12	A	705132	57	M	I	5'7"	45	16.18	8/4/2019	11:35AM	11:55AM	1:45PM	2PM	2:25	66	16	98	137	85	105	2	3	56	61	54	56	86	67	52	51	51	52	51	52	50
13	A	704610	37	F	I	5'3"	70	28.45	9/4/2019	1:10PM	1:35PM	3:20PM	3:30PM	2:20	83	18	98	131	82	104	2	0	67	77	70	66	61	90	73	80	56	52	56	57	60
14	B	705179	57	M	I	5'10"	82	26.79	10/4/2019	1:30PM	1:45PM	3PM	3:15PM	1:45	82	16	99	136	91	107	1	2	62	70	75	72	68	66	63	66	70	74	73	74	67
15	C	499283	28	M	I	5'10"	65	21.24	25/4/19	9:50AM	10:30AM	12:10PM	12:30PM	2:40	96	16	100	130	87	98	3	3	85	80	115	90	90	88	84	82	78	77	82	84	82
16	A	719246	47	F	I	5'5"	75	28.62	1/5/2019	12PM	12:40PM	3:45PM	4PM	4	62	16	100	132	96	108	2	2	70	72	71	64	66	72	65	60	56	58	60	62	65
17	C	705884	21	M	II	5'8"	70	24.22	1/5/2019	1:45PM	2:14PM	3:45PM	4PM	2:15	106	16	97	130	68	96	1	0	78	76	72	84	82	84	86	90	88	92	94	88	90
18	D	705116	45	F	II	5'2"	54	22.5	2/5/2019	8:45AM	9:30AM	1:00PM	1:15PM	4:30	**86**	18	98	138	78	105	0	0	62	64	62	60	76	78	76	78	79	76	78	80	81
19	D	716854	48	M	II	6'2"	85	29.72	2/5/2019	11:30AM	12:15PM	3:20PM	4PM	4:30	90	16	100	134	96	112	1	1	62	82	86	92	94	95	92	94	94	95	93	90	89
20	A	720631	35	M	II	5'4"	66	25.78	3/5/2019	9:20AM	9:40AM	11:00AM	11:20AM	2	78	16	96	138	78	105	3	3	82	86	84	80	81	82	84	94	96	92	93	94	95
21	C	720743	58	M	II	5'8"	80	27.68	3/5/2019	11:30AM	12:00PM	2:00PM	2:15PM	2:45	62	16	99	132	86	102	1	0	52	58	61	78	80	71	80	82	84	83	82	80	82
22	B	712664	35	M	II	5'9"	65	21.2	3/5/2019	12:30PM	1:00PM	2:15PM	2:30PM	2	98	16	100	118	76	92	1	2	86	80	82	85	91	92	85	80	82	89	85	82	86
23	A	720753	60	M	I	5'6"	65	19.7	6/5/2019	10:15AM	10:38AM	1:00PM	1:15PM	3	90	16	97	138	78	105	0	2	92	98	99	92	96	96	95	93	94	91	90	95	93
24	C	720803	28	M	I	5'8"	70	24.22	6/5/2019	10:00AM	10:30AM	12:45PM	1:00PM	3	92	16	98	136	78	104	1	0	80	68	72	74	76	79	76	112	121	89	92	93	92
25	B	496809	58	M	II	5'10"	65	22.22	6/5/2019	9:30AM	10:00AM	11:10AM	11:30AM	2	92	16	100	132	92	106	2	2	96	102	106	101	94	96	92	85	80	81	84	83	73
26	B	587506	33	M	I	5"10"	62	20.26	7/5/2019	1:05PM	1:30PM	3:15PM	3:30PM	2:25	68	18	98	132	96	108	2	2	56	54	52	66	68	69	72	74	72	73	78	75	76
27	D	722855	38	F	II	5'2"	60	25	7/5/2019	12:15PM	12:45PM	4:15PM	4:30PM	4:15	92	16	99	126	89	102	0	0	68	64	62	74	76	72	82	60	64	64	63	68	69
28	A	723179	30	M	II	5"9"	66	22.37	7/5/2019	1:25PM	2:00PM	3:30PM	3:45PM	2:20	92	16	97	138	88	106	3	3	88	92	91	90	102	106	82	86	84	85	87	92	90
29	A	723546	59	F	II	5'3"	67	26.5	8/5/2019	1:15PM	1:35PM	3:30PM	3:45PM	2:30	64	16	98	120	70	72	2	3	62	68	72	74	70	68	66	69	72	71	74	72	76
30	D	713247	18	M	I	6'	85	26.23	8/5/2019	10AM	10:30AM	12:15PM	12:30PM	2:30	92	18	98	136	82	96	2	2	56	54	62	64	76	94	101	100	92	94	88	85	90
31	B	588803	58	M	II	5'10"	55	17.97	8/5/2019	9:30AM	9:55AM	12:20PM	12:30PM	3	62	16	96	110	70	92	2	2	64	68	72	74	76	72	70	71	72	73	74	70	71
32	C	717601	25	M	II	6'	75	23.14	9/5/2019	10:25AM	10:40AM	3:45PM	4PM	5:35	120	16	95	132	83	102	0	1	92	102	102	106	102	92	88	78	76	78	78	76	79
33	D	713058	60	M	I	5'6"	58	21.32	9/5/2019	10:10AM	10:40AM	2:10PM	2:30PM	4:20	76	18	97	106	75	78	0	1	54	53	52	51	62	66	68	68	72	68	66	67	86
34	D	29908	49	F	I	5'4"	65	25.39	10/5/2019	11:30AM	12:30PM	4:15PM	4:30PM	5	77	16	99	128	70	90	0	0	68	86	85	83	90	81	82	79	79	80	79	76	74
35	B	698057	42	M	II	5'10"	75	24.51	10/5/2019	9:20AM	9:50AM	1:40PM	2PM	4:40	72	18	96	126	86	98	0	2	70	66	68	74	78	82	86	80	78	76	66	68	67
36	A	48344	44	M	II	5'10"	75	24.5	11/5/2019	12:45PM	1:15PM	5:10PM	5:30PM	4:45	78	16	100	140	82	96	2	3	80	76	79	82	80	76	74	70	72	71	70	69	72
37	C	726132	40	M	II	6'	85	26.23	11/5/2019	9:40AM	10:15AM	12:15PM	12:30PM	2:50	92	18	99	136	70	102	2	1	68	64	62	63	69	72	74	76	78	74	72	72	71
38	C	717629	22	M	I	5'9"	80	27.11	13/5/19	11:15AM	11:40AM	12:45PM	1PM	1:45	78	16	98	130	70	96	1	0	62	68	76	82	84	74	76	79	82	86	89	92	74
39	B	683683	23	M	I	5'9"	70	23.48	13/5/19	9:45AM	10:30AM	2PM	2:15PM	4:30	82	16	96	132	62	93	1	2	55	56	68	80	67	78	83	84	82	82	90	82	82
40	D	718529	40	F	II	5'2"	48	20	13/5/19	9:40AM	10:10AM	1:40PM	2PM	4:20	86	18	97	138	78	102	0	0	62	60	61	55	52	56	58	64	68	70	71	72	73
41	B	727077	47	M	II	5'8"	80	27.68	13/5/19	9:10AM	9:40AM	12:30PM	1PM	3:50	76	16	98	138	70	98	3	2	68	61	64	70	72	74	76	80	84	82	86	78	79
42	B	721648	41	F	II	5'8"	76	25.68	13/5/19	12PM	12:30PM	3:40PM	4PM	4	78	18	98	110	72	92	2	1	74	76	72	71	70	68	69	76	78	82	98	112	76
43	C	683780	28	M	II	5'2"	68	28.33	13/5/19	1:45PM	2:15PM	4:25PM	4:45PM	3	110	18	98	124	78	98	0	1	92	93	87	85	89	85	82	84	88	86	84	82	81
44	A	727122	31	M	II	5'11"	85	27.15	14/5/19	12PM	12:30PM	2PM	2:15PM	2:15	62	16	100	132	82	102	2	3	56	70	90	110	85	88	87	88	85	86	82	81	78
45	A	727711	33	M	II	5'11"	80	25.55	14/5/19	9:50AM	10:10AM	11AM	11:15AM	1:25	88	16	99	132	86	65	3	2	92	94	112	118	96	92	88	82	81	74	73	76	78
46	A	717668	35	M	II	5'6"	60	20.33	15/5/19	11:30AM	12:20AM	2:35PM	2:45PM	3:15	68	18	98	118	78	92	3	2	69	72	71	76	78	80	78	76	77	76	74	75	76
47	A	397598	21	M	I	5'10"	70	22.87	15/5/19	12:30PM	1:10PM	2:15PM	2:45PM	2:15	75	16	99	112	70	68	3	2	74	75	76	80	82	89	82	84	84	82	80	76	74
48	C	721471	38	M	II	5'11"	78	24.92	15/5/19	10AM	11:15AM	3:30PM	3:40PM	5:40	110	18	100	137	96	102	0	0	90	91	82	90	82	92	93	93	92	90	91	92	91
49	A	676472	58	M	II	5'5"	62	23.66	15/5/19	9:30AM	9:55AM	1PM	1:30PM	4	85	16	98	110	70	82	2	3	84	82	84	83	84	82	95	90	91	92	93	86	85
50	A	545193	22	M	I	5'9"	78	26.44	16/5/19	3:40PM	4:30PM	5:15PM	5:30PM	1:50	74	16	99	132	86	107	3	3	72	82	116	118	86	80	82	80	81	82	81	78	77
51	A	726177	44	M	II	5'10"	66	21.56	16/5/19	12:30PM	1:20PM	3PM	3:15PM	2:45	117	18	97	122	80	76	2	2	110	111	98	94	92	90	91	90	88	87	86	85	86
52	B	724184	24	M	I	5'11"	76	24.75	17/5/19	9AM	10AM	1:15PM	1:30PM	4:30	117	18	98	136	92	102	1	2	95	103	109	122	116	119	120	108	106	104	102	102	108
53	A	729777	56	F	II	5'2"	62	25.83	17/5/19	10:30AM	11:20AM	5:10PM	5:30PM	7	118	18	99	138	88	108	1	3	114	116	117	116	115	110	96	94	93	94	92	96	98
54	A	730788	30	M	I	5'11"	85	27.15	18/5/19	10:30AM	11AM	2:10PM	2:30PM	4	68	14	98	118	76	82	3	2	72	71	70	74	76	74	72	78	79	80	80	79	68
55	C	274282	39	F	I	5'6"	68	24.13	21/5/19	11:50AM	12:20PM	1:30PM	1:40PM	1:50	92	16	100	128	70	91	0	3	62	56	52	56	58	56	62	58	62	65	80	62	52
56	C	729967	25	M	II	5'11"	85	26.2	22/5/19	8:30AM	8:50AM	10:40AM	10:50AM	2:20	94	18	98	136	79	104	0	0	66	68	62	74	78	72	70	72	76	78	82	86	88
57	D	547480	58	M	II	6'	82	24.7	22/5/19	10AM	10:25AM	1:15PM	1:30PM	3:30	69	18	99	136	60	92	0	0	76	72	65	64	75	74	72	71	76	78	72	84	86
58	A	720274	58	M	II	6'	85	26.23	24/5/19	9:45AM	10:25AM	1:15PM	1:30PM	3:45	76	16	99	135	81	98	2	3	80	79	76	74	72	71	82	81	90	90	91	90	89
59	B	397529	42	F	I	5'3"	69	28.04	28/5/19	10:30AM	11:00AM	12:30PM	12:40PM	2:10	72	16	98	118	62	85	0	1	62	61	60	59	58	62	66	68	69	70	71	70	72
60	C	739113	48	F	I	5'2"	69	28.75	31/5/19	10:15AM	11:00AM	12:25PM	12:35PM	2:20	109	16	100	128	74	97	0	2	69	69	70	80	66	67	80	98	87	74	72	79	88
61	A	739863	53	F	I	5'5"	72	27.48	1/6/2019	3:40PM	3:50PM	4:50PM	5:00PM	1:20	102	16	96	137	96	102	2	3	103	89	82	83	129	113	99	106	97	85	82	85	83
62	D	133348	36	F	II	5'4"	65	25.39	1/6/2019	1:20PM	1:50PM	2:50PM	3:00PM	1:40	82	16	99	138	88	107	0	0	66	65	63	62	60	59	58	56	72	70	69	68	74

| | | |

			IVE MONITORING																																							
			Hg) Diastolic										NIBP(mmHg)MAP																													
Sr. No	Group	MRD No	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min
1	A	530507	59	54	66	59	64	110	91	92	92	77	84	103	102	103	94	79	70	129	128	93	74	80	71	84	81	82	121	114	111	107	95	99	100	100	100	100	100	100	100	100
2	D	636731	70	73	88	110	92	92	86	92	92	91	128	143	131	123	106	164	165	129	181	151	125	105	99	109	121	111	107	123	111	107	108	100	100	100	100	100	100	98	98	99
3	D	498498	64	68	68	88	93	100	93	86	91	92	107	107	110	113	102	116	115	102	110	92	84	79	80	79	105	106	114	107	100	114	107	98	98	97	98	99	99	99	99	99
4	A	640208	71	64	107	124	123	118	118	108	115	112	104	95	89	111	105	94	174	125	113	102	97	93	93	135	157	154	143	143	137	136	134	100	100	100	100	100	100	100	100	100
5	D	637747	51	55	54	69	91	75	76	78	84	80	98	90	76	85	108	125	141	120	82	72	67	80	77	74	88	117	94	92	96	101	99	98	99	100	100	100	100	99	99	99
6	C	638859	51	55	54	69	91	75	76	80	78	84	78	96	96	99	82	77	74	97	97	84	76	80	77	74	88	117	94	92	99	96	101	98	99	100	100	100	100	100	100	100
7	B	704418	72	91	86	78	79	75	56	86	85	83	98	102	108	107	105	98	106	86	70	100	99	82	107	97	99	100	98	71	101	98	96	100	100	100	100	100	100	99	99	99
8	D	647802	57	52	53	62	76	67	69	67	60	59	89	90	92	102	66	65	117	103	94	80	71	69	63	63	76	87	79	78	80	74	71	98	99	99	100	100	100	100	100	100
9	B	339375	40	47	86	59	54	59	55	56	86	42	85	88	83	63	72	125	99	97	107	104	88	68	74	101	81	84	90	76	83	101	66	97	98	100	100	100	100	98	98	98
10	C	654177	59	55	68	67	67	59	60	57	54	50	94	83	81	60	48	75	126	110	100	94	88	83	77	84	81	83	71	77	70	68	63	99	99	99	99	99	98	98	99	99
11	C	149379	70	88	82	87	77	76	66	63	65	65	94	118	93	92	101	92	89	113	108	106	103	85	106	97	105	91	86	84	74	82	79	100	100	100	100	100	100	100	100	100
12	A	705132	53	52	62	88	88	85	85	81	88	77	96	95	83	79	137	130	96	79	73	69	70	67	66	76	102	105	105	97	95	102	89	99	98	98	98	98	98	100	100	97
13	A	704610	56	79	91	84	86	85	86	91	88	76	99	100	102	101	98	86	133	104	82	70	105	71	95	107	100	101	98	106	107	104	86	97	97	100	100	100	100	100	99	99
14	B	705179	95	93	74	67	64	62	62	66	81	84	122	118	84	94	82	73	68	65	76	81	103	111	111	90	78	78	76	74	80	98	101	98	98	99	99	100	100	100	100	100
15	C	499283	51	54	92	77	74	76	66	77	110	91	87	84	80	106	72	73	73	89	83	78	75	68	79	111	95	103	103	84	95	121	114	100	100	100	100	100	100	100	100	100
16	A	719246	72	73	83	88	87	82	89	81	77	93	120	92	90	127	103	86	85	96	97	90	95	92	90	98	102	103	99	106	98	104	112	99	100	100	100	100	100	100	99	99
17	C	705884	92	79	78	110	80	110	79	90	77	79	85	87	87	98	104	105	96	111	121	98	105	110	106	105	121	103	121	106	110	98	105	99	100	100	100	100	100	100	100	100
18	D	705116	95	79	92	97	94	78	93	79	78	90	106	100	95	114	122	113	112	110	106	107	104	113	106	110	122	117	105	118	106	105	110	97	98	98	98	99	99	100	100	100
19	D	716854	68	64	64	71	88	64	68	64	68	71	85	87	81	106	102	110	107	92	84	79	107	79	79	79	92	105	83	80	79	80	92	99	100	100	100	100	100	100	100	100
20	A	720631	107	79	94	79	97	94	85	93	95	79	111	113	111	107	106	121	123	128	143	125	174	135	106	117	106	122	117	108	118	113	106	99	99	99	99	99	99	98	98	98
21	C	720743	77	75	76	70	85	86	75	77	88	93	81	84	79	114	107	107	107	100	96	107	107	104	100	101	96	106	107	100	104	107	112	99	99	99	99	99	99	99	99	99
22	B	712664	54	49	92	77	88	76	92	85	86	74	81	87	78	104	106	103	102	111	106	104	84	79	70	111	104	107	103	111	106	107	92	100	100	100	100	100	100	100	100	100
23	A	720753	75	77	68	44	75	77	79	83	77	75	106	114	103	102	94	99	96	92	91	93	103	100	104	92	96	100	101	93	103	104	100	98	98	98	99	99	99	100	100	100
24	C	720803	77	83	75	75	77	64	75	77	75	88	81	89	95	113	102	97	93	165	151	123	109	104	103	100	97	104	93	97	104	100	109	100	100	100	100	100	100	100	100	100
25	B	496809	78	63	78	53	91	45	80	76	84	66	71	82	80	107	103	111	79	81	82	92	101	96	84	96	77	114	82	99	92	101	78	99	99	99	100	100	100	100	100	100
26	B	587506	77	75	77	75	110	92	88	110	79	85	87	81	78	129	125	128	121	111	110	106	111	98	100	104	100	121	111	110	121	106	106	100	100	100	100	100	100	100	100	100
27	D	722855	62	52	57	59	52	76	78	78	76	67	100	87	81	111	100	76	104	107	94	66	79	76	65	69	71	63	87	92	90	87	94	99	99	99	100	100	100	100	100	100
28	A	723179	88	93	100	93	86	91	92	86	71	68	113	107	78	75	102	110	92	84	79	80	80	105	106	114	107	110	114	107	110	92	80	100	100	100	100	100	100	100	100	100
29	A	723546	78	77	79	85	79	90	83	75	57	69	95	89	97	93	104	105	93	93	107	114	116	105	104	106	106	104	110	103	100	78	87	99	99	99	99	100	100	100	100	100
30	D	713247	77	77	79	75	77	88	93	68	62	57	78	76	77	106	104	107	104	98	103	100	96	98	98	104	100	104	107	112	75	81	78	100	100	100	100	100	100	100	100	100
31	B	588803	60	59	79	58	86	70	62	74	52	64	102	110	80	72	99	106	90	80	90	94	85	87	90	102	85	99	94	87	97	82	88	99	99	99	99	99	99	99	98	98
32	C	717601	64	61	64	61	60	61	51	60	56	56	102	105	88	76	62	91	87	86	87	83	92	89	89	89	88	86	87	78	85	81	81	100	100	100	100	100	100	100	100	100
33	D	713058	71	72	68	60	67	69	68	89	72	71	75	63	61	87	92	91	102	99	93	86	92	97	92	80	75	87	89	87	102	92	94	100	100	100	100	100	100	100	100	100
34	D	29908	71	69	66	70	63	55	64	61	57	72	86	65	93	93	106	105	84	83	80	79	102	85	85	78	83	77	78	83	75	73	88	99	99	99	100	100	100	100	100	100
35	B	698057	56	56	61	63	60	67	72	66	68	68	110	90	99	85	94	82	85	105	102	89	85	81	81	89	87	85	79	84	76	83	79	100	100	100	100	100	100	100	100	100
36	A	48344	70	72	70	69	67	71	86	75	62	60	102	110	111	117	115	107	119	115	97	99	102	93	91	92	89	87	94	99	89	70	75	98	98	98	98	98	98	99	99	99
37	C	726132	71	69	71	75	68	62	68	76	74	72	79	79	68	66	83	83	111	107	110	91	92	97	89	94	89	80	70	80	89	84	84	99	99	99	100	100	100	100	100	100
38	C	717629	67	73	75	86	89	72	72	71	86	68	96	102	101	90	79	83	84	90	110	102	89	85	90	89	99	102	92	91	94	99	87	100	100	100	100	100	100	100	100	100
39	B	683683	52	53	49	57	63	61	60	58	58	59	88	93	93	65	84	84	99	97	89	87	84	81	80	81	84	81	80	78	77	80	77	99	99	99	100	99	100	100	100	100
40	D	718529	98	78	82	72	73	74	68	78	82	77	77	76	83	66	61	79	89	117	107	115	117	119	102	115	90	89	84	79	98	100	107	100	100	100	100	100	100	100	100	100
41	B	727077	75	75	72	73	76	77	73	71	73	75	92	91	89	86	87	82	87	104	106	107	95	100	95	92	93	96	99	93	91	93	95	98	99	99	100	100	100	100	100	100
42	B	721648	81	69	68	73	68	89	86	70	72	72	77	75	81	100	47	87	89	83	79	84	123	117	89	87	90	79	102	99	93	92	91	100	100	100	100	100	100	100	100	100
43	C	683780	71	70	86	70	72	72	86	71	70	71	116	100	89	88	91	109	101	98	85	98	91	94	92	99	93	92	91	99	91	92	94	100	100	100	100	100	100	100	100	100
44	A	727122	72	71	70	70	67	70	74	74	68	73	103	125	139	130	117	107	101	98	96	86	85	87	94	89	92	85	93	97	84	83	89	100	100	100	100	100	100	100	100	100
45	A	727711	69	69	68	70	89	72	74	70	96	92	105	96	115	106	103	98	101	102	99	93	92	87	89	87	89	102	91	97	93	102	110	100	100	100	100	100	100	100	100	100
46	A	717668	70	75	89	86	70	72	86	77	79	71	87	84	77	83	100	87	104	106	85	90	94	92	89	102	99	93	92	99	98	104	95	99	99	99	100	100	100	100	100	100
47	A	397598	69	70	67	67	61	62	57	57	69	68	103	87	85	91	99	93	91	94	97	93	94	89	89	85	87	72	81	78	77	87	79	99	99	99	99	99	99	99	99	99
48	C	721471	71	69	69	68	70	71	79	85	93	88	110	99	102	89	70	80	72	75	105	76	87	95	87	89	87	93	95	104	106	112	107	98	98	98	99	99	100	98	98	97
49	A	676472	86	89	70	67	72	71	70	74	70	71	90	89	98	84	79	84	83	80	76	80	90	99	102	92	85	92	94	93	97	93	97	98	98	99	99	99	100	100	100	100
50	A	545193	70	78	77	78	88	77	83	80	62	83	102	108	116	120	92	93	100	92	91	99	102	92	102	107	105	107	98	103	103	85	103	100	100	100	100	100	100	100	100	100
51	A	726177	61	70	72	72	71	68	72	69	57	75	95	98	85	87	89	110	99	102	89	70	80	72	73	92	91	94	87	90	87	78	87	100	100	100	100	100	99	99	99	99
52	B	724184	88	85	77	80	70	89	83	77	70	90	92	78	90	115	102	119	115	117	108	118	112	107	106	98	103	93	103	103	98	96	110	98	98	98	98	99	99	99	99	99
53	A	729777	88	93	85	79	80	79	78	95	90	90	117	111	115	119	123	119	115	111	117	111	113	107	112	106	104	103	106	105	113	111	110	99	99	99	100	100	100	100	100	100
54	A	730788	62	73	78	72	70	72	72	70	71	70	87	75	77	78	76	89	94	110	103	100	85	81	89	98	90	93	91	92	93	94	93	98	98	98	99	99	99	99	99	99
55	C	274282	74	88	73	70	59	58	62	60	52	62	85	90	88	85	106	102	88	82	80	94	105	96	116	94	97	90	99	86	87	80	87	100	100	100	100	100	100	100	100	100
56	C	729967	82	58	60	52	64	70	88	74	62	62	89	80	91	92	91	110	102	102	119	115	99	105	85	87	80	88	90	116	96	86	87	99	99	99	99	99	99	99	99	99
57	D	547480	72	70	72	71	70	71	68	69	67	71	123	117	111	107	119	115	119	102	102	110	102	92	93	91	94	92	97	87	89	87	94	99	99	99	99	99	99	99	99	99
58	A	720274	56	93	85	90	95	92	94	85	93	75	119	132	123	115	117	111	107	102	101	85	87	76	118	108	111	113	114	117	108	112	87	99	100	100	100	100	100	100	100	100
59	B	397529	43	74	72	78	83	62	75	62	68	86	106	104	107	77	87	75	103	78	93	91	80	68	84	84	98	103	85	87	81	80	99	98	98	99	100	100	100	100	100	100
60	C	739113	92	66	64	60	58	59	57	66	84	72	82	82	80	83	72	70	105	128	118	86	77	106	86	84	79	76	76	65	84	100	89	100	100	100	100	100	100	100	100	100
61	A	739863	71	65	66	68	75	90	80	92	90	91	109	129	101	116	162	161	115	102	112	98	87	84	83	80	81	94	118	109	121	119	114	96	98	98	99	99	100	100	100	100
62	D	133348	97	75	77	85	80	79	77	72	70	74	84	79	77	77	76	89	92	110	108	107	103	122	100	104	106	103	104	98	91	93	97	99	99	100	100	100	100	100	100	100

																ADVERSE EFFECTS									
			SPO2(%)													Bradycardia (HR<50/min)			Hypotension_ (SBP<90mmHg or DBP<60mmHg)			Tachycardia_ (HR> 20% of baseline value) and Hypertension (blood pressure > 20% of baseline value)			
Sr. No	Group	MRD No	9 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	Bradycardia _Number of episodes	Bradycardia _Treatment given(iv)	Bradycardia Dose of drug administered (mg)	Hypotension_Number of episodes	Hypotension_Treatment given(iv)	Hypotension Dose of drug administered(mg)	Tachycardia_ Number of episodes-Tachycardia	Tachycardia Number of episodes-Hypertension	Tachycardia and Hypertension-Treatment given(iv)	Tachycardia-Dose of drug administered(ug)
1	A	530507	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	1	EPHEDRINE	6	1	1	FENTANYL	60
2	D	636731	98	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	1	1	FENTANYL	70
3	D	498498	99	99	99	99	99	99	99	99	98	98	99	99	0	0	0	0	0	0	0	0	0	0
4	A	640208	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	2	3	FENTANYL	270
5	D	637747	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	1	EPHEDRINE	6	1	1	FENTANYL	50
6	C	638859	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	80
7	B	704418	99	99	99	99	99	99	99	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
8	D	647802	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	5	EPHEDRINE	30	0	0	0	0
9	B	339375	98	99	99	99	99	99	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
10	C	654177	100	100	100	100	100	100	100	100	100	99	99	99	0	0	0	3	EPHEDRINE	18	0	0	0	0
11	C	149379	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
12	A	705132	97	97	97	97	97	97	97	97	97	97	97	97	1	ATROPINE	0.5	0	0	0	0	0	0	0
13	A	704610	99	99	99	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
14	B	705179	99	99	98	98	98	98	98	99	99	99	99	99	0	0	0	1	EPHEDRINE	6	0	0	0	0
15	C	499283	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
16	A	719246	99	98	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
17	C	705884	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
18	D	705116	100	100	100	98	98	98	98	98	98	98	98	99	0	0	0	0	0	0	0	0	0	0
19	D	716854	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
20	A	720631	99	99	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
21	C	720743	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
22	B	712664	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
23	A	720753	100	98	98	98	98	98	98	98	98	98	98	99	0	0	0	0	0	0	0	0	0	0
24	C	720803	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
25	B	496809	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
26	B	587506	100	98	98	98	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	1	FENTANYL	70
27	D	722855	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	5	EPHEDRINE	30	0	0	0	0
28	A	723179	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
29	A	723546	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
30	D	713247	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
31	B	588803	98	98	98	98	98	98	98	98	98	98	98	98	0	0	0	0	0	0	1	1	FENTANYL	60
32	C	717601	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
33	D	713058	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
34	D	29908	100	100	100	100	100	100	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
35	B	698057	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
36	A	48344	99	98	98	99	99	98	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
37	C	726132	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
38	C	717629	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
39	B	683683	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
40	D	718529	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
41	B	727077	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
42	B	721648	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	2	2	FENTANYL	80
43	C	683780	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
44	A	727122	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
45	A	727711	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	0	FENTANYL	80
46	A	717668	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
47	A	397598	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
48	C	721471	97	97	97	97	97	97	97	97	97	98	98	98	0	0	0	0	0	0	0	0	0	0
49	A	676472	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
50	A	545193	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	80
51	A	726177	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
52	B	724184	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
53	A	729777	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
54	A	730788	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
55	C	274282	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
56	C	729967	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
57	D	547480	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
58	A	720274	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	1	FENTANYL	90
59	B	397529	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
60	C	739113	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
61	A	739863	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	80
62	D	133348	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0

									Anaesthesia Start		Surgery Start	Surgery Finish	Anaesthesia finish	Duration	BASELINE VITALS						GRADE OF MYOCLONUS		HR(Per min)															
																					Grade																	
Sr. No	Group	MRD No	Age(yrs)	Sex	ASA Grading	Height(ft and inches)	Weight (kg)	BMI	Date	Time	Time	Time	Time	Time	HR(bpm)	RR (per min)	SPO2(%)	SBP(mmhg)	DBP(mmhg)	MAP (mmhg)	0-1min	1-2 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min
63	C	360293	30	F	I	5'2"	57	23.75	3/6/2019	9:10AM	9:40AM	12:50PM	1:00PM	3:50	63	16	98	107	71	86	1	2	67	77	64	67	70	72	90	86	80	72	71	70	68
64	B	740491	35	M	II	5'6"	65	24.8	3/6/2019	9:20AM	9:40AM	1:45PM	2:00PM	4:40	68	15	98	120	79	97	1	2	64	66	67	66	61	58	70	72	73	74	72	79	74
65	D	739677	51	M	II	5'10"	72	23.52	3/6/2019	1:00PM	1:25PM	2:20PM	2:30PM	1:30	96	16	98	133	79	100	0	0	66	62	59	56	52	51	54	64	68	66	66	64	65
66	B	740420	34	F	II	5'5"	78	29.77	4/6/2019	1:05PM	1:30PM	2:15PM	2:30PM	1:25	90	16	98	132	79	100	2	2	78	76	66	70	72	74	74	71	76	72	70	92	91
67	C	460513	43	M	II	5'11"	62	19.8	4//6/19	10:00AM	10:40AM	11:20AM	11:30AM	1:30	78	16	100	133	94	109	0	1	60	62	58	56	58	58	62	61	60	60	66	62	63
68	D	741480	22	M	I	5'7"	58	20.86	4/6/2019	12:30PM	1:00PM	3:10PM	3:15PM	2:45	96	18	98	124	72	92	0	0	56	54	52	52	52	56	58	64	62	60	61	60	62
69	B	741283	44	M	II	5'10"	90	29.41	5/6/2019	11:30AM	12:00PM	12:50PM	1:00PM	1:30	69	16	98	125	90	105	0	2	62	60	59	58	62	61	70	70	68	64	66	72	70
70	B	742080	36	F	II	5'2"	64	26.66	5/6/2019	9:15AM	9:40AM	10:20AM	10:30AM	1:15	96	16	99	137	85	105	1	2	91	79	90	72	86	87	82	80	83	82	77	83	83
71	A	448445	59	M	I	5'6"	71	26.1	6/6/2019	9:45AM	10:00AM	12:35PM	12:45PM	3	80	16	100	126	84	103	2	3	86	82	89	84	82	80	81	69	70	72	74	78	80
72	B	740938	46	M	II	5'7"	78	28.05	6/6/2019	2:45PM	3:15PM	3:50PM	4:00PM	1:15	90	16	98	135	74	99	2	2	76	72	74	72	70	68	66	70	72	68	78	74	66
73	C	743234	35	M	I	5'11"	80	25.55	6/6/2019	1:45PM	2:10PM	3:10PM	3:30PM	1:45	84	16	98	139	89	112	0	1	62	60	58	59	54	52	50	66	62	62	61	60	60
74	B	744111	45	F	II	5'3"	58	23.57	8/6/2019	9:15AM	10:00AM	12:00PM	12:15PM	3	117	16	98	137	94	107	0	0	102	93	75	72	74	69	86	80	78	77	74	70	75
75	B	744333	50	F	I	5'4"	55	21.48	8/6/2019	11:30AM	12:00PM	1:35PM	1:45PM	2:15	98	16	100	126	82	96	1	2	96	92	90	68	69	76	84	86	90	91	90	90	90
76	A	743224	60	F	II	5'2"	65	27.08	10/6/2019	1:50PM	2:05PM	2:50PM	3:00PM	1:10	92	18	97	132	86	107	1	3	94	92	96	102	106	92	94	96	98	99	100	101	102
77	D	746105	58	F	II	5'5"	76	29	11/6/2019	9:30AM	10:00AM	11:00AM	11:10AM	1:40	86	16	98	126	89	102	0	0	48	46	72	70	68	69	60	62	56	55	56	54	55
78	D	5941	42	F	I	5'6'	75	27.57	11/6/2019	2:15PM	2:30PM	4:00PM	4:15PM	2	76	16	100	124	78	98	1	0	56	54	58	56	58	68	69	70	52	57	58	59	62
79	B	746269	55	F	I	5'2"	70	29.16	12/6/2019	5:10PM	5:40PM	7:20PM	7:30PM	2:20	76	18	99	126	64	92	1	2	62	60	62	64	96	109	118	126	82	80	68	66	64
80	A	746434	49	F	I	5'2"	70	29.16	12/6/2019	4:50PM	5:00PM	7:50PM	8:10PM	3:20	92	18	99	120	64	92	2	2	92	90	91	106	108	110	138	126	124	96	94	92	90
81	C	745660	35	F	II	5'4"	65	25.59	12/6/2019	4:10PM	4:30PM	5:30PM	5:45PM	1:35	86	18	98	136	66	95	1	0	68	66	62	60	61	60	58	54	52	52	51	56	58
82	C	747282	35	F	I	5'4"	72	28.12	14/6/19	9:50AM	10:10AM	11:15AM	11:30AM	1:40	78	18	97	135	74	99	0	0	64	68	62	62	60	61	62	68	66	66	64	64	62
83	B	747439	42	F	II	5'2"	54	22.5	14/6/19	2:45PM	3:00PM	4:40PM	5:00PM	2:15	82	18	98	120	73	97	2	0	62	61	60	58	70	72	76	74	72	73	64	62	60
84	C	747999	21	F	I	5'3"	50	20.32	14/6/19	12:00PM	12:30PM	1:35PM	1:45PM	1:45	110	16	98	128	81	97	0	1	116	119	120	118	111	111	107	107	105	105	106	107	107
85	C	747878	30	M	I	5'10'	80	26.14	14/6/19	9:30AM	10:05AM	12:15AM	12:30AM	3	72	16	99	128	90	109	1	1	62	54	62	80	65	62	80	60	69	70	73	72	65
86	B	747791	50	M	I	5'11'	89	28.43	15/6/19	12:00PM	12:40PM	2:35PM	2:45PM	2:45	92	16	100	127	78	97	2	1	76	72	70	68	62	64	66	70	70	71	72	80	82
87	D	746977	45	F	I	5'3"	69	28.04	15/6/19	2:00PM	2:45PM	3:05PM	3:15PM	1:15	96	16	98	132	82	102	0	1	61	69	62	61	60	64	62	62	64	60	72	74	72
88	A	130458	60	F	I	5'2"	62	25.83	17/6/19	11:15AM	11:30AM	12:10PM	12:15PM	1	90	18	98	135	74	99	2	3	94	92	90	88	88	101	102	102	102	130	132	126	102
89	C	749694	27	M	II	5'7"	60	21.58	18/6/19	12:00PM	12:30PM	1:50PM	2:00PM	2	86	18	99	124	72	92	0	0	62	60	61	62	62	63	70	71	72	70	70	62	64
90	B	708844	36	F	II	5'6"	80	29.41	18/6/19	12:05PM	12:30PM	2:45PM	3:00PM	2:55	90	18	98	129	75	97	1	2	68	69	70	71	74	76	78	79	80	81	81	82	82
91	A	749626	43	F	I	5'8"	78	21.58	18/6/19	10:00AM	10:15AM	10:50AM	11:00AM	1	90	16	99	126	87	101	2	3	92	94	92	96	94	96	102	96	92	94	90	86	84
92	A	751474	53	M	II	5'11"	90	28.75	21/6/19	9:30AM	9:45AM	11:00AM	11:15AM	1:45	88	18	99	112	58	80	2	3	86	88	92	96	92	90	91	90	86	82	81	80	82
93	B	751874	30	F	II	5'5"	70	26.71	21/6/19	9:55AM	10:10AM	11:20AM	11:30AM	1:35	86	16	100	112	58	80	2	1	76	80	72	76	78	80	72	88	98	96	90	92	86
94	D	747295	58	M	I	5'11"	74	23.64	21/6/19	9:55AM	10:10AM	12:50PM	1:00PM	2:55	86	16	97	118	69	89	0	0	62	44	42	72	74	76	74	72	70	66	64	64	62
95	D	751884	31	F	I	5'3"	60	24.39	21/6/19	10:00AM	10:30AM	11:45AM	12:00PM	2	68	16	98	132	68	84	0	0	54	56	52	52	72	74	76	78	60	62	61	60	62
96	C	752743	45	F	II	5'3"	69	28.04	22/6/19	9:00AM	9:30AM	1:35PM	1:45PM	4:45	78	18	99	136	77	104	0	0	64	62	60	58	56	56	55	58	62	61	62	62	62
97	A	738945	35	M	I	5'10"	86	28.1	24/6/19	2:55PM	3:15PM	4:05PM	4:15PM	1:20	76	16	99	127	64	86	2	3	78	78	86	88	99	132	134	110	91	90	76	74	72
98	D	753551	35	F	I	5'3"	72	28.1	24/6/19	9:40AM	10:15AM	11:15AM	11:30AM	1:50	76	16	98	133	82	103	0	0	60	58	52	54	52	46	72	66	64	62	60	58	52
99	D	725491	45	M	I	5'8"	70	24.22	24/6/19	1:20PM	1:30PM	2:30PM	2:40PM	1:20	88	18	98	118	78	96	0	0	60	64	59	70	60	80	69	68	62	61	60	61	62
100	B	753692	19	M	I	6'2"	86	25.14	24/6/19	9:30AM	10:15AM	12:15PM	12:30PM	3	70	16	99	124	74	94	0	0	66	70	73	66	56	68	80	80	74	73	72	66	62
101	B	754409	49	F	II	5'4"	66	25.78	26/6/19	9:40AM	9:55AM	1:15PM	1:30PM	3:50	102	16	99	128	79	99	0	2	68	67	66	65	66	66	64	62	66	60	59	58	60
102	C	635101	37	F	I	5'4"	70	27.34	28/6/19	9:30AM	10:00AM	10:50AM	11:00AM	1:30	92	18	100	131	86	104	0	1	68	64	62	60	61	60	62	64	66	68	69	64	64
103	C	791755	55	F	II	5'2"	60	25	21/8/19	12:30PM	12:50PM	2:10PM	2:30PM	2	96	16	98	135	80	101	0	0	74	70	98	120	90	86	85	84	80	78	78	78	76
104	A	790531	33	F	I	5'2"	57	23.75	21/8/19	11:25AM	12:00PM	12:45PM	1PM	1:35	115	18	99	132	87	109	3	2	103	103	102	112	109	109	108	107	106	104	102	105	101
105	D	250922	42	F	I	5'2"	60	25	23/8/19	1:00PM	1:15PM	2:05PM	2:15PM	1:15	66	18	98	125	77	95	0	1	66	63	64	64	62	62	63	63	63	67	67	67	68
106	A	792186	60	M	II	5'7"	75	26.97	23/8/19	10:15AM	10:55AM	12:00PM	12:15PM	2	62	16	99	130	92	104	2	3	68	70	72	60	54	55	56	54	56	54	52	54	56
107	B	792636	38	F	I	5'4"	62	24.21	23/8/19	12:50PM	1:10PM	1:45PM	2PM	1:10	76	18	100	114	52	74	1	2	78	110	90	86	80	82	82	81	80	80	80	80	80
108	D	793206	47	F	I	5'3"	57	23.17	24/8/19	10:40AM	11:00AM	12:20PM	12:30PM	1:50	96	16	99	136	78	103	0	1	70	66	52	54	48	56	78	80	80	82	82	82	82
109	D	794988	46	M	I	5'8"	80	27.68	26/8/19	9:00 AM	9:30AM	10:45AM	11:00AM	2	78	18	99	132	76	100	0	0	62	60	60	61	62	62	60	60	66	68	68	64	62
110	D	794240	60	F	I	5'2"	60	25	26/8/19	9:30AM	9:50AM	11:50AM	12:00PM	2:30	80	18	96	126	64	92	0	0	62	60	58	56	54	58	59	60	60	60	60	61	61
111	D	30807	34	F	II	5'3"	65	26.42	27/8/19	1:35PM	1:45PM	3:15PM	3:30PM	1:55	90	18	95	136	74	95	1	0	72	70	70	71	72	72	70	71	70	70	70	70	70
112	C	752638	36	F	II	5'5"	70	26.71	27/8/19	11:30AM	11:45AM	1:20PM	1:30PM	2	78	18	97	138	72	97	1	1	78	76	70	71	72	78	86	110	90	80	80	81	80
113	D	796757	60	F	I	5'3"	62	25.2	28/9/19	2:15PM	2:25PM	4:15PM	4:30PM	2:15	82	18	99	124	70	93	0	0	66	70	71	71	72	70	68	64	65	66	68	70	72
114	C	791367	50	F	II	5'4"	63	24.6	28/9/19	9:05AM	9:15AM	11:30AM	11:45AM	2:40	86	18	100	116	60	88	1	2	72	70	71	72	74	74	76	78	74	74	72	70	70
115	B	796782	20	M	I	5'9"	58	19.66	28/8/19	2:50PM	3:00PM	3:30PM	3:50PM	1	82	18	99	124	70	93	2	1	74	70	72	70	70	70	71	72	72	72	74	76	74
116	C	634505	47	F	I	5'4"	70	27.34	28/8/19	10:45AM	10:50AM	11:40AM	11:45AM	1	70	18	98	124	78	98	1	2	66	64	62	60	62	62	60	62	58	60	60	60	62
117	C	619012	48	M	I	5'10"	70	22.87	28/8/19	9:45AM	9:55AM	10:50AM	11:00AM	1:15	94	16	98	136	66	95	1	2	80	77	72	70	92	120	90	87	85	84	85	83	78
118	D	797789	48	F	I	5'2"	64	26.66	29/8/19	11:50AM	12:00PM	1:50PM	2:00PM	2:10	94	16	97	134	82	104	0	1	72	80	82	97	87	89	91	88	85	78	78	81	81
119	D	796984	53	M	I	5'11"	80	25.55	29/8/19	3:20PM	3:30PM	4:20PM	4:30PM	1:10	80	18	100	120	66	92	0	1	78	76	74	74	72	70	72	74	76	78	76	76	76
120	B	798060	51	M	I	5'11"	84	26.83	29/8/19	2:00PM	2:10PM	3:20PM	3:30PM	1:30	84	16	98	136	83	103	0	1	72	77	77	84	82	83	88	90	77	87	90	90	90

																																															INTRAOPERAT
											NIBP (mmHg) Systolic																																						NIBP(mm
Sr. No	Group	MRD No	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min
63	C	360293	62	63	66	61	62	63	64	64	114	125	112	110	108	111	123	111	118	128	114	115	125	122	118	117	125	121	121	113	115	71	79	68	68	67	68	90	74	76	85	62
64	B	740491	71	72	70	69	68	68	67	66	119	115	114	110	139	144	147	149	143	130	117	115	124	133	109	125	117	115	119	108	105	73	76	74	52	84	89	90	90	86	87	76
65	D	739677	65	70	71	76	76	74	74	73	118	115	121	121	125	143	151	121	113	111	118	116	112	110	109	147	138	139	136	138	136	73	75	79	76	73	88	89	79	74	74	74
66	B	740420	90	88	82	76	80	81	80	80	126	116	122	124	125	113	117	114	103	105	113	132	138	135	141	137	141	134	124	119	114	93	84	78	83	91	63	76	74	50	56	63
67	C	460513	64	66	66	66	66	62	61	60	135	136	137	116	141	141	139	146	154	156	148	149	144	141	155	147	141	138	132	124	122	100	97	95	84	98	96	104	104	103	103	99
68	D	741480	61	60	60	60	60	60	61	61	110	118	112	136	108	103	102	102	106	81	93	104	122	120	76	114	112	108	109	127	97	67	69	67	74	62	56	62	64	72	52	66
69	B	741283	71	69	68	66	62	64	63	61	121	114	124	108	108	136	134	120	118	123	121	116	120	123	121	121	117	127	132	123	121	94	76	75	56	53	70	80	76	75	76	80
70	B	742080	90	90	91	88	98	87	91	93	134	133	124	130	159	133	141	119	114	117	108	108	156	153	144	150	140	151	137	136	134	76	79	75	83	76	87	103	64	76	59	53
71	A	448445	81	80	82	82	83	81	83	82	136	139	138	132	129	128	126	120	123	128	128	129	130	126	124	125	128	129	122	116	117	92	94	88	84	79	77	74	75	77	77	79
72	B	740938	62	64	62	68	72	71	70	76	107	111	81	125	76	129	115	129	121	119	118	107	115	131	103	98	111	117	114	115	112	61	66	52	85	52	80	73	79	76	73	75
73	C	743234	60	62	62	61	61	62	64	68	133	143	139	138	123	118	132	139	138	139	117	119	121	129	133	127	145	116	120	120	114	85	90	87	87	76	75	85	88	83	89	72
74	B	744111	72	74	70	68	64	64	60	68	149	120	108	88	96	104	151	137	114	96	89	85	99	122	117	112	104	101	96	94	102	101	68	71	56	59	67	108	105	71	58	50
75	B	744333	91	92	90	91	92	90	90	90	120	119	141	137	139	122	121	128	117	137	137	126	118	123	127	125	125	125	116	117	112	83	77	98	97	83	84	71	84	68	90	95
76	A	743224	100	100	96	92	94	90	91	90	131	130	116	142	121	125	113	130	137	125	130	124	119	113	121	115	96	116	112	115	113	86	90	81	95	78	85	75	80	96	86	87
77	D	746105	58	59	60	61	62	60	60	60	115	80	107	102	117	122	106	75	93	95	136	143	132	132	127	110	107	110	107	108	126	75	50	56	64	72	73	64	53	66	69	74
78	D	5941	60	61	61	61	60	60	60	60	108	98	95	100	126	113	102	116	111	120	110	109	118	108	107	112	116	127	126	120	127	62	67	66	66	64	53	64	60	59	73	67
79	B	746269	66	69	70	71	72	74	74	76	108	100	126	135	129	166	153	146	116	120	125	115	132	118	109	134	126	133	124	119	128	70	59	64	74	75	107	82	98	66	79	73
80	A	746434	86	84	82	81	80	78	78	77	119	115	135	125	120	118	175	166	167	153	146	116	114	112	107	124	118	110	112	126	124	57	73	81	73	79	62	111	107	101	82	98
81	C	745660	59	60	62	61	60	61	62	62	100	112	114	105	107	96	97	108	107	108	106	104	100	93	102	112	108	103	120	109	108	59	67	73	67	71	61	62	56	57	62	64
82	C	747282	61	60	54	56	52	52	52	51	110	101	105	106	108	95	104	95	98	103	119	112	112	108	103	114	121	125	122	113	115	67	68	67	72	70	43	68	66	67	68	57
83	B	747439	61	60	61	62	62	62	62	62	106	105	97	110	118	128	108	105	139	146	143	137	121	112	119	102	103	102	98	102	100	72	67	62	67	69	74	64	63	78	98	77
84	C	747999	107	105	102	102	96	94	88	86	148	138	136	128	132	118	99	103	111	114	118	119	123	130	128	126	121	116	115	121	120	101	95	87	78	80	80	57	68	54	59	62
85	C	747878	55	57	59	62	61	64	62	62	124	119	121	110	118	108	121	133	113	109	105	103	70	125	117	115	111	115	115	114	116	83	82	73	52	72	64	87	79	63	59	56
86	B	747791	76	76	72	72	76	75	74	74	114	108	109	120	122	121	106	135	132	118	126	138	134	124	100	103	115	115	118	109	101	62	62	55	73	73	79	64	74	75	62	71
87	D	746977	71	72	71	70	69	68	68	64	151	143	148	151	139	117	108	107	105	103	98	95	135	143	122	125	120	121	115	113	122	98	100	80	81	78	72	64	63	64	63	67
88	A	130458	96	92	92	92	91	92	91	92	127	147	143	137	130	151	142	118	113	176	166	111	117	118	118	124	123	124	126	114	116	78	71	71	70	53	78	95	62	83	84	107
89	C	749694	62	61	60	60	60	60	60	60	116	108	101	96	108	107	108	104	99	102	105	115	121	125	135	114	113	107	107	112	109	66	56	68	60	62	56	66	67	63	72	63
90	B	708844	80	80	80	80	82	81	80	81	141	139	115	146	118	118	128	106	128	111	119	126	115	141	111	132	131	129	130	128	130	98	94	74	106	82	86	88	76	90	83	85
91	A	749626	88	84	86	88	89	90	91	92	114	119	120	105	122	119	109	113	122	120	114	129	117	123	114	131	120	118	115	125	114	83	81	89	77	87	78	69	84	61	81	77
92	A	751474	84	82	80	81	82	92	90	91	118	113	112	109	106	108	112	109	107	129	120	121	106	115	114	128	151	113	121	122	125	69	73	67	75	84	70	79	75	71	75	79
93	B	751874	82	84	81	88	82	84	82	76	102	105	98	92	94	75	88	98	138	120	107	120	121	129	127	122	115	121	108	109	108	51	56	54	53	56	36	47	63	89	66	54
94	D	747295	60	61	62	63	64	64	66	66	113	76	98	99	124	110	106	118	101	119	108	99	102	114	108	108	115	120	131	126	111	73	52	67	63	70	67	64	69	68	57	73
95	D	751884	62	62	61	60	60	60	60	60	96	118	121	113	112	131	143	141	117	127	127	108	130	113	125	109	112	116	103	104	105	60	69	71	73	67	92	71	72	64	74	64
96	C	752743	62	62	60	61	60	68	64	66	114	115	122	113	106	112	132	142	148	135	118	129	127	143	148	141	130	137	129	125	115	62	66	73	74	72	73	75	95	94	77	62
97	A	738945	71	72	71	72	72	72	72	71	102	126	132	138	136	176	160	151	148	143	142	130	127	108	120	113	106	115	108	105	107	64	71	75	78	77	84	96	81	80	77	73
98	D	753551	54	54	52	54	54	54	54	54	118	116	120	106	118	112	151	145	136	131	130	118	120	155	134	139	118	110	117	116	114	76	77	81	75	74	75	101	96	92	88	91
99	D	725491	69	69	64	65	64	60	62	64	116	120	115	134	79	132	115	125	105	97	94	89	105	98	97	99	97	111	111	112	109	75	82	84	88	60	107	81	90	67	63	62
100	B	753692	65	60	56	55	56	56	57	56	122	106	109	105	104	114	110	113	109	101	101	93	91	97	94	104	96	97	98	139	92	44	47	48	47	49	72	56	56	44	45	48
101	B	754409	62	62	64	64	65	66	66	68	119	113	122	153	156	141	123	121	131	128	126	145	133	138	149	142	145	148	148	130	122	75	74	69	99	91	90	80	79	83	83	74
102	C	635101	64	64	62	61	62	61	61	60	114	109	112	116	108	126	131	121	119	108	109	103	105	109	107	108	111	104	107	102	124	62	55	60	60	62	89	92	71	71	66	55
103	C	791755	76	72	74	74	74	74	72	72	137	136	187	107	167	133	122	126	123	126	116	138	129	121	131	114	112	127	120	118	132	96	94	124	70	94	76	66	74	77	75	73
104	A	790531	92	89	85	90	85	86	84	82	119	113	111	168	149	121	120	116	118	110	113	117	114	113	108	119	117	118	134	153	113	71	70	81	119	102	76	73	68	63	64	60
105	D	250922	68	67	66	62	64	66	68	68	116	111	104	98	96	91	91	89	92	92	116	121	116	123	128	118	123	105	99	95	94	80	65	62	56	52	51	49	45	47	54	74
106	A	792186	56	56	56	56	55	55	56	56	145	100	131	107	92	116	101	115	111	130	117	114	112	125	110	116	115	111	109	114	114	92	66	85	69	56	79	65	76	77	92	79
107	B	792636	81	81	79	78	78	78	78	74	119	176	120	120	97	126	116	117	116	109	116	129	108	118	112	108	102	101	111	105	109	54	98	56	75	55	75	73	54	54	50	55
108	D	793206	83	84	84	85	85	86	86	86	110	126	118	117	107	81	108	136	136	134	143	126	124	117	114	122	120	113	121	135	115	69	71	62	75	57	52	62	77	79	70	90
109	D	794988	62	61	61	60	60	61	62	60	120	106	107	118	111	122	125	126	121	115	124	107	106	122	115	132	110	134	135	132	136	79	64	57	62	75	73	73	71	79	73	78
110	D	794240	60	60	60	60	60	60	61	62	98	99	76	102	121	96	96	108	107	105	100	112	108	104	107	100	110	126	125	126	124	67	63	52	72	71	61	60	70	65	67	59
111	D	30807	71	70	70	70	71	70	71	71	127	108	137	136	126	125	124	124	121	135	127	129	114	112	120	120	119	116	115	114	125	64	56	66	66	89	86	70	72	71	74	78
112	C	752638	76	68	66	66	66	66	66	66	126	127	129	127	129	127	126	176	142	143	139	148	136	128	126	120	120	119	116	112	108	64	64	70	74	75	78	89	84	73	71	78
113	D	796757	72	70	70	71	72	72	74	72	118	113	112	108	108	81	105	102	105	105	124	109	110	118	119	112	108	115	121	115	106	69	73	67	70	73	52	67	64	64	63	70
114	C	791367	68	68	66	68	66	68	70	72	112	110	109	108	105	118	111	126	126	107	126	126	118	108	108	109	112	96	96	118	113	67	67	75	62	55	62	75	64	71	61	71
115	B	796782	74	74	72	72	72	72	72	72	116	112	111	118	101	112	109	105	126	110	117	127	127	122	114	120	109	108	105	102	102	60	60	75	62	68	67	57	55	71	60	64
116	C	634505	62	61	61	60	60	60	61	61	98	99	95	110	116	108	108	109	112	115	104	102	124	114	107	105	108	110	109	107	108	67	63	43	60	66	56	70	76	73	73	68
117	C	619012	77	76	77	77	76	76	76	76	151	146	128	132	132	192	148	139	130	124	123	124	120	149	138	137	136	130	137	124	118	103	91	86	88	93	123	99	91	83	79	77
118	D	797789	82	76	74	71	72	72	72	72	136	135	109	79	100	107	163	139	130	121	118	102	102	102	99	102	105	108	107	107	105	81	74	53	47	55	64	92	82	72	61	51
119	D	796984	74	74	74	74	74	72	72	72	96	96	110	106	115	125	122	126	129	120	136	127	114	107	122	121	119	124	110	103	100	61	60	67	64	75	73	73	64	70	73	79
120	B	798060	86	80	82	84	86	86	84	84	131	125	125	124	122	121	126	132	121	120	134	133	127	122	125	121	121	126	125	131	128	78	79	78	84	71	86	78	92	82	78	87

			IVE MONITORING																																				
			Hg) Diastolic										NIBP(mmHg)MAP																											
Sr. No	Group	MRD No	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	0 min	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min
63	C	360293	66	73	73	73	77	78	76	73	73	66	87	121	85	87	84	86	108	93	95	104	80	89	93	91	93	93	99	98	95	91	84	99	99	100	100	100	100	100	100	100
64	B	740491	76	83	79	59	78	76	80	82	64	56	93	96	94	67	111	116	117	116	109	100	99	96	102	105	86	99	99	93	99	84	81	98	98	99	99	100	100	100	100	100
65	D	739677	74	75	67	62	85	81	84	85	81	81	93	93	97	98	93	114	116	97	90	90	94	93	88	85	82	112	108	108	106	104	103	99	99	99	99	99	100	100	100	99
66	B	740420	87	96	100	98	95	97	80	75	64	76	110	99	96	102	113	91	99	94	73	81	91	103	113	115	113	110	114	106	94	90	96	99	99	99	100	100	100	100	100	100
67	C	460513	100	97	97	101	99	96	96	87	83	78	115	111	110	99	113	116	117	121	126	126	119	120	116	114	123	116	113	113	103	100	96	99	99	99	100	100	100	100	100	100
68	D	741480	68	73	79	52	73	73	73	76	78	62	85	89	87	95	90	85	79	80	90	66	75	83	91	97	61	92	90	91	94	97	70	99	99	100	100	100	100	100	100	100
69	B	741283	74	76	76	94	80	72	81	85	76	80	103	96	94	79	77	106	106	98	93	97	98	92	98	97	103	98	92	103	109	97	98	99	99	99	100	100	100	100	100	100
70	B	742080	56	96	76	61	68	68	70	76	70	80	103	101	94	102	110	109	121	90	96	86	77	79	121	113	107	108	104	117	110	106	106	99	99	99	100	100	100	100	100	100
71	A	448445	78	74	75	78	78	75	78	74	73	71	112	114	110	104	100	100	94	95	99	100	101	99	95	98	97	99	99	99	96	92	94	100	100	100	100	98	98	98	98	98
72	B	740938	74	69	81	64	67	66	72	62	66	63	76	86	66	100	61	101	89	102	94	94	94	82	90	103	80	83	86	90	80	84	80	99	99	100	100	100	100	100	100	100
73	C	743234	73	80	80	85	81	88	74	76	73	75	106	111	110	108	97	93	109	110	109	112	92	94	98	102	106	103	112	92	98	95	92	100	100	100	100	100	100	100	100	100
74	B	744111	50	69	78	74	70	64	61	60	58	64	121	88	86	69	74	78	130	118	87	73	66	66	81	96	94	88	80	79	72	72	80	98	98	98	100	100	100	100	99	99
75	B	744333	87	85	86	85	84	79	82	77	65	63	97	90	114	112	107	99	95	103	90	108	115	105	97	101	99	99	100	96	91	86	88	99	99	99	99	100	100	100	100	100
76	A	743224	70	71	78	71	75	60	71	73	66	74	107	107	96	111	96	103	90	102	102	99	104	93	94	91	97	95	75	92	90	84	90	98	98	99	99	99	99	99	100	100
77	D	746105	71	68	75	69	69	57	69	61	62	71	93	64	76	80	90	91	79	61	75	80	95	101	84	100	88	87	77	87	77	81	95	98	99	99	100	100	100	100	100	100
78	D	5941	75	62	70	71	73	66	69	64	83	69	81	83	76	83	94	80	80	88	88	97	85	89	85	88	90	90	89	88	92	96	88	100	100	100	100	100	100	100	100	100
79	B	746269	66	75	62	57	70	71	83	72	71	74	88	75	92	99	97	132	115	119	89	97	93	84	100	85	78	96	95	103	92	94	97	99	99	99	100	100	100	100	100	100
80	A	746434	66	73	73	65	72	69	67	67	86	70	83	89	98	93	97	85	138	132	123	115	119	89	92	90	82	92	89	85	87	99	93	99	99	99	100	100	100	100	100	100
81	C	745660	67	66	66	64	60	62	56	83	76	70	75	87	92	80	90	72	70	78	77	81	79	79	83	75	80	88	90	85	96	94	88	98	98	99	99	99	100	100	100	100
82	C	747282	60	60	66	56	62	79	73	73	74	75	85	80	80	90	88	68	83	76	83	79	83	93	88	90	85	80	97	93	91	90	93	100	100	100	100	100	100	100	100	100
83	B	747439	96	71	67	71	64	63	72	67	72	66	90	80	70	85	89	97	83	82	102	119	107	102	97	87	94	80	80	84	83	84	83	99	99	100	100	100	100	100	100	100
84	C	747999	64	70	77	78	76	72	74	66	73	76	122	114	110	108	112	99	76	86	87	96	98	100	105	108	109	108	105	88	91	97	98	99	99	100	100	100	100	100	100	100
85	C	747878	50	50	78	76	80	70	80	76	74	79	102	99	96	67	96	84	102	105	91	86	81	73	55	99	99	95	90	93	96	94	97	99	99	99	100	100	100	100	100	100
86	B	747791	78	70	78	66	64	73	70	70	75	68	80	90	89	97	91	97	79	99	100	85	95	105	96	98	83	80	89	89	92	89	80	100	100	100	100	100	100	100	100	100
87	D	746977	69	74	88	73	73	79	79	75	74	73	131	122	111	117	102	90	83	80	82	80	83	80	99	114	91	93	97	97	93	90	93	98	98	99	100	100	100	100	100	100
88	A	130458	59	72	69	70	70	72	72	71	73	66	97	95	94	100	90	99	113	85	103	119	132	88	90	89	92	93	91	92	95	92	89	99	99	99	100	100	100	100	100	100
89	C	749694	66	79	73	74	73	77	65	71	73	76	89	78	80	75	81	76	90	79	77	84	82	84	97	93	99	92	90	82	90	90	94	99	99	100	100	100	100	100	100	100
90	B	708844	87	81	97	81	92	92	78	88	86	93	116	112	87	120	97	99	102	88	105	93	98	102	93	117	94	107	107	101	103	102	107	99	99	99	100	100	100	100	100	100
91	A	749626	85	67	71	62	77	79	78	75	70	62	93	96	100	90	103	93	88	95	84	99	92	106	88	94	80	88	97	93	93	88	80	100	100	100	100	100	100	100	100	100
92	A	751474	79	64	66	62	100	89	74	79	73	73	89	90	87	89	93	88	92	88	90	97	97	97	79	84	80	111	116	90	97	91	93	100	100	100	100	100	100	100	100	100
93	B	751874	86	61	75	78	73	66	79	70	76	73	73	74	89	68	72	48	62	74	111	87	74	101	94	97	97	91	84	97	88	94	91	100	100	98	98	98	98	99	99	99
94	D	747295	63	72	62	62	70	73	83	77	71	75	90	61	83	77	93	85	79	89	80	83	87	77	84	80	81	88	89	96	98	95	87	100	100	100	100	100	100	100	100	100
95	D	751884	56	53	53	86	55	60	60	56	68	51	75	89	97	90	87	110	101	101	82	94	86	78	90	80	99	89	88	88	85	83	75	100	100	100	100	100	100	100	100	100
96	C	752743	75	78	77	80	72	53	70	70	86	73	80	84	91	90	90	90	100	113	117	101	85	97	97	107	111	101	90	100	95	99	89	100	100	100	100	100	100	100	100	100
97	A	738945	53	64	67	79	74	64	66	62	55	57	80	95	100	105	104	119	127	117	111	107	86	90	86	82	97	90	79	84	81	75	77	100	100	100	100	100	100	100	100	100
98	D	753551	81	79	107	96	96	77	76	75	78	78	93	92	98	86	93	89	117	117	109	105	105	96	97	122	111	113	94	88	94	93	92	98	98	98	99	99	99	99	99	99
99	D	725491	62	71	64	64	62	59	78	74	72	74	91	95	97	100	69	118	99	104	80	81	78	75	81	79	76	77	73	89	89	88	87	100	100	100	100	100	100	100	100	100
100	B	753692	45	47	52	49	52	48	54	52	106	52	83	76	79	78	75	88	85	87	78	75	69	67	66	72	68	80	74	73	74	110	69	100	100	100	100	100	100	100	100	100
101	B	754409	91	79	86	79	93	92	87	84	78	73	93	89	94	121	113	114	97	98	103	103	98	112	101	110	105	113	112	101	113	98	91	99	99	100	100	100	100	100	100	100
102	C	635101	56	55	57	56	62	75	67	74	72	78	80	89	88	88	90	102	110	97	94	90	89	85	75	78	76	81	87	79	84	84	98	100	100	100	100	100	100	100	100	100
103	C	791755	88	80	76	81	62	63	81	76	75	85	117	113	156	85	125	96	88	94	99	98	92	110	101	94	103	80	80	103	98	93	109	100	100	100	100	100	100	99	99	99
104	A	790531	64	71	71	70	82	81	74	93	107	70	90	86	82	139	118	97	91	88	88	83	87	89	88	87	85	96	96	89	108	124	86	100	100	100	100	100	100	100	100	100
105	D	250922	80	84	74	75	77	66	65	55	53	52	96	83	80	75	71	67	68	63	70	72	91	96	98	93	93	95	85	82	75	70	69	100	100	100	100	100	100	100	100	100
106	A	792186	78	75	84	69	80	80	77	76	75	80	109	78	101	85	69	94	80	95	90	104	95	90	91	99	89	94	93	91	88	91	92	99	99	100	100	100	100	98	98	99
107	B	792636	79	60	76	66	62	57	56	60	57	60	77	124	79	95	73	98	92	77	76	70	77	100	78	82	80	78	76	75	79	74	78	99	100	100	100	100	100	100	100	100
108	D	793206	71	78	72	62	73	79	74	79	81	75	87	95	85	87	77	66	81	104	104	96	110	95	98	90	80	91	97	90	97	98	93	99	100	100	100	100	100	100	100	100
109	D	794988	74	64	73	75	75	69	70	85	75	79	97	79	77	85	87	91	93	95	97	89	98	84	79	91	93	100	87	96	106	100	104	99	100	100	100	100	100	100	100	100
110	D	794240	73	73	67	74	66	60	64	86	89	70	83	77	61	84	97	72	75	88	82	80	75	90	91	79	84	83	78	92	99	102	93	98	98	99	99	100	100	100	98	98
111	D	30807	75	73	73	73	65	57	60	66	62	73	86	78	91	95	102	99	93	92	97	99	97	97	92	90	97	92	83	88	84	80	93	100	100	100	100	100	100	100	100	100
112	C	752638	80	66	74	89	83	73	57	60	60	64	92	86	95	94	97	97	102	119	86	101	102	111	95	97	102	96	97	83	88	93	83	100	100	100	100	100	100	100	100	98
113	D	796757	57	69	62	57	60	66	66	79	75	64	89	90	87	88	91	66	80	80	82	82	93	78	87	85	83	93	90	84	97	93	79	100	100	100	100	100	100	100	100	100
114	C	791367	89	70	66	62	55	60	61	60	70	73	87	85	89	81	75	85	87	92	95	77	95	102	92	90	90	89	93	72	75	92	90	100	100	100	100	100	100	100	100	100
115	B	796782	74	78	73	62	83	76	70	63	62	64	88	88	87	85	80	87	78	75	95	78	82	94	97	91	80	96	94	88	82	79	80	100	100	100	100	100	100	100	100	100
116	C	634505	72	78	73	71	67	62	69	57	56	64	83	77	68	78	89	78	88	94	90	89	83	84	98	92	90	80	81	87	78	76	83	100	100	100	100	100	100	100	100	100
117	C	619012	76	79	103	72	70	74	53	66	78	62	123	113	103	106	111	150	114	108	102	98	96	94	97	128	97	100	95	90	91	98	85	100	100	100	100	100	100	100	100	100
118	D	797789	43	56	55	60	58	64	73	71	65	67	108	93	81	60	74	91	103	106	98	90	85	71	81	78	78	74	83	91	90	82	80	100	100	100	100	100	100	100	100	100
119	D	796984	78	73	74	73	79	68	70	67	64	66	72	75	85	79	93	93	91	92	95	97	104	97	92	84	91	97	87	93	85	80	83	98	99	100	100	100	100	100	100	98
120	B	798060	80	69	73	73	79	71	89	86	92	74	100	98	97	102	91	100	99	108	96	94	102	104	88	91	93	97	97	102	99	110	97	99	99	100	100	100	100	100	100	100

																ADVERSE EFFECTS										
			SPO2(%)													Bradycardia (HR<50/min)			Hypotension_ (SBP<90mmHg or DBP<60mmHg)			Tachycardia_ (HR> 20% of baseline value) and Hypertension (blood pressure > 20% of baseline value)			
Sr. No	Group	MRD No	9 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	Bradycardia _Number of episodes	Bradycardia _Treatment given(iv)	Bradycardia Dose of drug administered (mg)	Hypotension_Number of episodes	Hypotension_Treatment given(iv)	Hypotension Dose of drug administered(mg)	Tachycardia_ Number of episodes-Tachycardia	Tachycardia Number of episodes-Hypertension	Tachycardia and Hypertension-Treatment given(iv)	Tachycardia-Dose of drug administered(ug)
63	C	360293	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	0	FENTANYL	60
64	B	740491	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	1	FENTANYL	70
65	D	739677	99	99	99	99	99	99	99	99	100	100	100	100	0	0	0	0	0	0	0	0	0	0
66	B	740420	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
67	C	460513	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
68	D	741480	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
69	B	741283	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
70	B	742080	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
71	A	448445	98	98	98	98	98	98	98	98	98	98	98	98	0	0	0	0	0	0	0	0	0	0
72	B	740938	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
73	C	743234	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
74	B	744111	99	99	98	98	99	99	99	99	99	99	99	99	0	0	0	3	EPHEDRINE	18	0	0	0	0
75	B	744333	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
76	A	743224	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
77	D	746105	100	100	100	100	100	100	100	100	100	100	100	100	1	ATROPINE	0.5	2	EPHEDRINE	12	0	0	0	0
78	D	5941	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
79	B	746269	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
80	A	746434	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
81	C	745660	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
82	C	747282	100	98	98	98	98	98	98	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
83	B	747439	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
84	C	747999	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
85	C	747878	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
86	B	747791	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
87	D	746977	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
88	A	130458	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
89	C	749694	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
90	B	708844	100	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
91	A	749626	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
92	A	751474	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
93	B	751874	99	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
94	D	747295	100	100	100	100	100	100	100	100	100	100	100	100	2	ATROPINE	1	1	EPHEDRINE	6	0	0	0	0
95	D	751884	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
96	C	752743	100	100	99	99	98	98	98	98	98	98	98	98	0	0	0	0	0	0	0	0	0	0
97	A	738945	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	90
98	D	753551	99	99	99	99	99	99	99	99	99	99	99	99	1	ATROPINE	0.5	0	0	0	0	0	0	0
99	D	725491	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	2	EPHEDRINE	12	0	0	0	0
100	B	753692	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
101	B	754409	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	1	FENTANYL	70
102	C	635101	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
103	C	791755	99	99	99	97	97	97	97	96	97	97	98	98	0	0	0	0	0	0	0	0	0	0
104	A	790531	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
105	D	250922	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
106	A	792186	99	99	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
107	B	792636	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
108	D	793206	100	98	98	99	99	99	99	99	100	100	100	100	1	ATROPINE	0.5	1	EPHEDRINE	6	0	0	0	0
109	D	794988	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
110	D	794240	97	97	97	97	98	99	99	99	100	100	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
111	D	30807	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
112	C	752638	98	98	98	98	98	98	98	98	99	99	99	99	0	0	0	0	0	0	1	1	FENTANYL	70
113	D	796757	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
114	C	791367	98	98	99	99	99	99	99	99	99	99	99	99	0	0	0	0	0	0	0	0	0	0
115	B	796782	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
116	C	634505	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0
117	C	619012	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	1	1	FENTANYL	70
118	D	797789	100	99	99	98	98	98	99	99	99	99	100	100	0	0	0	1	EPHEDRINE	6	0	0	0	0
119	D	796984	98	99	98	98	98	98	99	99	100	100	100	100	0	0	0	0	0	0	0	0	0	0
120	B	798060	100	100	100	100	100	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0

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Date 9/9/19

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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Richa Jindal**, a student of your college for **MD Anaesthesiology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

To study comparative efficacy with three different doses of dexmedetomidine for prevention of etomidate induced myoclonus

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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh
Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

Doctor of Medicine

In

ANAESTHESIOLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

August, 2018

Dr. Richa Jindal

DEPARTMENT OF ANAESTHESIOLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

LUDHIANA, PUNJAB-141001

ABSTRACT OF PLAN OF THESIS

Title	TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS
For the degree of	M.D. Anaesthesiology
Name of the candidate	Dr Richa Jindal
Supervisor	Dr. Sandeep Kundra, Associate Professor, Department of Anaesthesia, DMCH, Ludhiana
Co-supervisor	Dr. Neeru Luthra, Associate Professor, Department of Anaesthesia, DMCH, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Etomidate is an intravenous anaesthetic agent which provides stable hemodynamics. However, the high incidence of myoclonus is a problem which can lead to muscle fiber damage and myalgias. Various agents like midazolam, opioids, magnesium sulphate and atracurium have been used to reduce it. Dexmedetomidine, an α_2 agonist has also been used for prevention of etomidate induced myoclonus, but there is still no consensus on the safe and effective dose for this purpose.

Aim of study: To study comparative efficacy with three different doses of dexmedetomidine pretreatment on incidence and severity of etomidate-induced myoclonus.

Materials and methods: ASA I and II patients aged 18-60 years scheduled for elective surgery under general anaesthesia will be enrolled in this prospective, randomized, double blinded study after an informed written consent.

Patients will be randomly allocated to four groups of 30 patients each using a computer-generated table of random numbers. Group A patients will be administered 10 ml of isotonic saline, Groups B, C and D will be given dexmedetomidine 0.25 μg kg^{-1}, 0.5 μg kg^{-1} and 1 μg kg^{-1} respectively. All the drugs will be diluted in 10 ml saline and administered over 10 mins. Once the infusion is completed, 0.3 mg kg^{-1} etomidate will be injected intravenously over a period of 30 sec and the patients will be observed for the incidence and grade of myoclonus for next two min.

Clinical significance: Myoclonus can lead to myalgias, elevated serum potassium and increased chances of reflux aspiration. Significance of this study is to reduce these complications.

Keywords: Dexmedetomidine, Etomidate, Myoclonus.

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CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled "**TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS"** exist in the Department of Anaesthesiology at Dayanand Medical College and Hospital, LUDHIANA and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate herself under our supervision and guidance.

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6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Etomidate is a short acting, non-barbiturate, imidazole derivative intravenous anaesthetic agent that allows rapid induction and recovery after a single dose. Due to its stable hemodynamic profile and minimal effect on respiratory system as compared to other induction agents, it is preferred in patients with underlying cardiac disease, intracranial hypertension and in patients with shock.[1] Pain on induction, phlebitis and myoclonus are the most common side effects of etomidate.[2] The occurrence of phlebitis and injection pain have been abolished by the fat emulsion, but the incidence of myoclonus is still as high as 50%–80%.[2,3]

The consequences of myoclonus can be especially serious in non-fasting patients for emergency surgery, patients with open eye injury, poor cardiovascular reserve, as it can lead to muscle fiber damage, myalgias, elevated serum potassium levels and increased chances of reflux aspiration.[2] Although etomidate-induced myoclonus in most patients is temporary, it is extremely harmful in patients with hypertension, aneurysms, and coronary heart disease and can be life threatening.[2] In addition, during the jerky movements ECG leads can get detached resulting in delay in monitoring.[1] The mechanism of these myoclonic movements is not clear, but some studies have suggested that it may be a kind of seizure activity due to finding of increased delta waves on EEG recording.[1] Others have opined that myoclonus is a result of subcortical disinhibition like that of restless leg syndrome during sleep and does not happen from epileptic focus.[1,3] A number of drugs like midazolam, opioids, magnesium sulphate and

rocuronium have been investigated to reduce the rate and intensity of this adverse effect.[1] Dexmedetomidine, an α_2 agonist having anaesthesia-sparing, analgesic and anxiolytic properties has also shown promise in reducing the incidence of etomidate induced myoclonus.[1,3] Dey et al compared dexmedetomidine in a dose of 0.5 µg kg^{-1} with midazolam (0.015 mg kg^{-1}); and found it to reduce the incidence and severity of myoclonus, but with increased incidence of adverse effects like hypotension and bradycardia.[4] Luan et al used dexmedetomidine in two doses (0.5 µg kg^{-1} and 1µg kg^{-1}) and the incidence of myoclonus was reduced, but with hypotension and bradycardia was more with a dose of 1 µg kg^{-1}. This was expected as the hypotension and bradycardia with dexmedetomidine has earlier been reported to be dose dependent.[3] Thus, a need is felt to find minimal effective dose of dexmedetomidine so that myoclonus is avoided and adverse effects associated with higher doses of dexmedetomidine are avoided. The present study is, therefore planned to compare the effects of three different dexmedetomidine doses of 0.25 µg kg^{-1}, 0.5 µg kg^{-1} and 1 µg kg^{-1} for prevention of etomidate induced myoclonus.

6.2 REVIEW OF LITERATURE

Etomidate induced myoclonus still remains an unsolved mystery as the exact mechanism of its occurrence and ideal agent for its prevention remains elusive. The high incidence of myoclonus to the tune of 80 % is a cause for concern in non pre-medicated patients.[2,3] A variety of drugs have been investigated for their ability to suppress these myoclonic movements which includes benzodiazepines, opioids, magnesium sulphate, IV lignocaine, gabapentin, thiopental , propofol and pretreatment with muscle relaxants.[5-18]

The incidence and intensity of myoclonus has been reported to be dependent on dose and speed of injection with lower incidence of myoclonus when smaller doses of etomidate are injected slowly.[19]

Pre-treatment with midazolam has been widely used and found to be effective in mitigating myoclonic movements induced by etomidate.[5] Similarly opioids have also been found to be effective in reducing the incidence of myoclonic movements associated with etomidate use.[6]

Abbas et al conducted study on two hundred and eighty four patients scheduled for elective orthopedic surgery to compare the effect of midazolam, magnesium sulphate, remifentanil and low dose etomidate and found remifentanil to be more effective than midazolam for this effect.[7]

Similarly Isitemiz et al have used combination of fentanyl in a dose of 0.5 µg kg^{-1} and midazolam 0.015 mg kg^{-1} and reported that the combination reduced the incidence of myoclonus by 65.2%.[8]

Alka et al used combination of butorphanol 0.02 mg kg^{-1} and midazolam 1 mg to compare with fentanyl and midazolam combination and reported that the

butorphanol and midazolam combination reduced incidence of myoclonus by 3.3% than fentanyl and midazolam combination.[9]

Wang et al studied oxycodone 0.1 mg kg^{-1} and fentanyl 1µg kg^{-1} for this purpose and reported the incidence in oxycodone group as 0.0%.[10]

Mayank et al conducted prospective, randomized, double blind study on one hundred patients to study the effect of nalbuphine 0.2 mg kg^{-1} and found it to be effective in reducing incidence of etomidate induced myoclonus by 52% than normal saline group. [11]

Yu et al performed meta-analysis of six Randomized control trials (RCT) and concluded that preinjection of dezocine is effective in lowering the incidence and severity of etomidate induced myoclonus without increasing etomidate induced dizziness and nausea. [12]

The major problem with both midazolam and opioids is that these drugs result in respiratory depression and desaturation especially at high doses.[1] This has prompted researchers to try other drugs with more desirable properties to reduce etomidate induced myoclonic movements.

Gupta et al found that IV lignocaine in a dose of 1 mg kg^{-1} reduced the incidence of myoclonus by 10% as compared to placebo in a study conducted on two hundred patients who were divided into four groups to receive placebo and three different doses of lignocaine.[13]

Mensure et al noted that oral gabapentin in dose of 800 mg and 1200 mg as premedication to be effective in reducing the incidence of myoclonus as compared to placebo group but no significant difference in the incidence of myoclonus was found when groups receiving oral gabapentin in dose of 400mg and placebo were compared. [14]

Liu et al conducted a prospective, double blind, randomized controlled study on three sixty-three patients scheduled for a short duration, painless gastrointestinal endoscopy in which pretreatment with different doses of propofol was done before induction with etomidate and found that the incidence and severity of etomidate induced myoclonus was lower in patients receiving pretreatment with propofol as compared to patients receiving etomidate alone.[15]

Dexmedetomidine is now a days being widely used in anaesthesia and critical care practice due to many desirable properties. It has sedative and analgesic properties without causing any respiratory depression. Many investigators have found it to prevent etomidate induced myoclonus as well.[1,3]

Mizrak et al conducted a prospective, randomized, double - blind study comparing the effect of pretreatment with dexmedetomidine 0.5 µg kg^{-1}, thiopental 1 mg kg^{-1} and saline on incidence of etomidate induced myoclonus and postoperative pain at 30 minutes and found incidence and intensity of myoclonus significantly lower in dexmedetomidine and thiopental groups than in control group but postoperative pain score at thirty minutes was significantly higher in thiopental group than dexmedetomidine and control group.[16]

Dey et al compared 0.5 µg kg^{-1} dexmedetomidine and 0.015 mg kg^{-1} midazolam for prevention of etomidate –induced myoclonus and noted that incidence of myoclonus was reduced by 17.5% in patients treated with dexmedetomidine.[4]

Du et al have also reported the efficacy of dexmedetomidine to reduce myoclonus due to etomidate. [2]

Though the effectiveness of dexmedetomidine in suppressing myoclonus has been widely reported but the appropriate dose for this is still under debate.

Dixit et al [1] administered dexmedetomidine in a dose of 1 µg kg^{-1} while Dey et al [4] used 0.5 µg kg^{-1}. Luan et al compared 0.5 µg kg^{-1} with 1 µg kg^{-1} and found dexmedetomidine at these doses to be effective. The incidence of hypotension and bradycardia was found to be higher with 1 µg kg^{-1} of dexmedetomidine.[3]

Dexmedetomidine has been used in doses ranging from 0.25-1.0 µg kg^{-1} for suppression of laryngoscopic response and there is benefit in choosing the smallest dose as the adverse effects are dose dependent.[20]

6.3 AIMS AND OBJECTIVES OF THE STUDY

To study comparative efficacy with three different doses of dexmedetomidine pretreatment on incidence and severity of etomidate- induced myoclonus.

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

The study will be conducted in a prospective, randomized, double blinded manner in the department of Anaesthesiology, DMCH Ludhiana after obtaining clearance from hospital ethics committee. 120 adult patients of either sex between age group 18 to 60 years belonging to ASA grade I or II scheduled for elective surgery under general anaesthesia will be randomly allocated to either of four study groups of 30 patients each.

Group Allocation

Patients will be randomly allocated to either of four groups as per computer generated random numbers which will be kept in a sealed envelope and opened at the end of study. The study drug will be prepared in a coded manner by an anaesthesia resident who will not participate in the management of patient.

Group A patients will be administered 10ml of isotonic saline.

Group B patients will be administered dexmedetomidine 0.25 µg kg^{-1} in 10 ml isotonic saline over 10 mins.

Group C patients will be administered dexmedetomidine 0.5 µg kg^{-1} in 10 ml isotonic saline over 10 mins.

Group D patients will be administered dexmedetomidine 1µg kg^{-1} in 10 ml isotonic saline over 10 mins.

Number of Cases

Total number of cases proposed to be studied will be 120 with 30 patients in each group.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA:

Patients of either sex between age group 18 to 60 years belonging to ASA grade I or II with BMI <30 kg/m^2 and scheduled for elective surgery under general anaesthesia will be included in study.

EXCLUSION CRITERIA:

1. Patients with BMI>30kg/m^2.
2. Patients with Bradycardia (HR < 60/min), having heart blocks, on β–blockers or having pacemakers.
3. Known case of hypoadrenalism or patients on steroid medication.
4. H/o asthma, chronic cough or upper respiratory infection two weeks before surgery.
5. H/o any neurologic disease.
6. H/o any psychiatric disorders.
7. Pregnant and lactating patients.
8. H/o any drug allergy.
9. Patients having uncontrolled diabetes or hypertension.
10. Patients who have received benzodiazipines or opioids within the previous 24 hrs.
11. Any evidence of sepsis.

Preanaesthetic check up

A thorough preanaesthetic check up will be conducted preoperatively one day prior to surgery comprising of detailed history, general physical and systemic examination. Routine investigations like complete hemogram, prothrombin

time/INR, urine routine, renal function tests, random blood sugar, chest X-ray and ECG will be obtained.

Premedication

All patients will be kept nil per oral for at least six hours prior to surgery. Patient will be counselled and explained regarding the surgical procedure to allay anxiety. No pharmacological anxiolytic therapy will be administered. All patients will be given Tab Ranitidine 150 mg a night prior to the surgery.

ANAESTHESIA TECHNIQUE

After arrival of patient to the operating room, routine monitoring such as electrocardiogram (ECG), non-invasive blood pressure (NIBP), heart rate (HR) and arterial oxygen saturation (SpO_2) will be started and baseline parameters will be recorded. A 20-gauge Intravenous (IV) cannula will be secured and I/V fluid infusion started. Before anaesthesia induction, all patients will be administered study drug over 10 mins as per group allocation. Group A will be infused 10ml of isotonic saline, while Groups B, C and D will be infused 0.25, 0.5 and 1.0 µg kg^{-1} dexmedetomidine in 10ml isotonic saline respectively over 10 mins. Once the infusion is completed, this time will be labelled as '0' and 0.3 mg kg^{-1} etomidate will be injected intravenously over a period of 30 sec.

Patients will be observed continuously for myoclonus for 2 min by an anaesthesia resident blinded to study drug received. Myoclonic movements will be defined as involuntary, short duration muscular contractions leading to short observable movements in parts of the body.

The intensity of myoclonus will be graded as:[1]

0- No myoclonus

1- mild myoclonus (short movements of a body segment, e.g. a finger or a wrist only)
2- moderate myoclonus (mild movements of two different muscles, e.g. face and leg)
3- severe myoclonus (intense clonic movements in two or more muscle groups, e.g. fast adduction of a limb)

After administration of etomidate and evaluation for myoclonus, all patients will be injected with 2 μg kg^{-1} fentanyl and isoflurane 1% will be started. To facilitate tracheal intubation injection atracurium 0.5 mg kg^{-1} will be given. Trachea will be intubated with appropriate sized cuffed tube. After ensuring correct endotracheal tube placement, all patients will be mechanically ventilated and maintained on O_2: N_2O and Isoflurane. Intraoperatively management of anaesthesia will be as per the discretion of anaesthetist managing the case.

Hemodynamic parameters will be recorded every 1 minute for initial 10 minutes and then every 5 minutes till the end of 60 minutes. Hypotension will be defined as systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg and an intravenous injection of 6mg ephedrine will be administered. Bradycardia will be defined as HR <50 beats per minute and any episode of bradycardia will be treated with I/V injection of 0.5 mg atropine. An episode of tachycardia (defined as heart rate > 20% of baseline value) and hypertension (defined as blood pressure > 20% of baseline value), lasting for more than a minute, will be controlled by a bolus of fentanyl (1 μg kg^{-1}) given intravenously. Another bolus of 0.5 μg kg^{-1} fentanyl may be repeated after 15 minutes if the episode of heart rate and blood pressure does not revert to

normal. More fentanyl boluses may be given if the attending anaesthesiologist who is blinded to the study infusion feels the need for it.

Outcome

The following parameters will be statistically analysed:

1) Incidence of etomidate induced myoclonus.

2) Grading of etomidate induced myoclonus.

3) Incidence of any adverse effects.

Statistical Analysis

Data will be described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using ANOVA. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. A probability value (p value less than 0.05 will be considered statistically significant All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes

Group A patients will be given 10ml isotonic saline.

Group B patients will be given dexmedetomidine 0.25 µg kg^{-1} in 10ml isotonic saline over 10 mins.

Group C patients will be given dexmedetomidine 0.5 µg kg^{-1} in 10ml isotonic saline over 10 mins.

Group D patients will be given dexmeditomidine 1 µg kg^{-1} in 10ml isotonic saline over 10 mins.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Applied for

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INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Supervisor **Signature of Candidate**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"TO STUDY COMPARATIVE EFFICACY WITH THREE DIFFERENT DOSES OF DEXMEDETOMIDINE FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ